PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 38/00, 47/12, C07C 229/00, 233/00, 317/14, C07D 209/02, 239/02, 241/02, 257/04, 311/04

A1

(11) International Publication Number: WO 98/34632

(43) International Publication Date: 13 August 1998 (13.08.98)

(21) International Application Number: PCT/US98/02619

(22) International Filing Date: 6 February 1998 (06.02.98)

(30) Priority Data:

08/796,336	7 February 1997 (07.02.97)	US
08/796,340	7 February 1997 (07.02.97)	US
08/796,338	7 February 1997 (07.02.97)	US
08/797,813	7 February 1997 (07.02.97)	US
08/797,816	7 February 1997 (07.02.97)	US
08/797,820	7 February 1997 (07.02.97)	US
08/797,100	7 February 1997 (07.02.97)	US
08/796,337	7 February 1997 (07.02.97)	US
08/796,334	7 February 1997 (07.02.97)	US
08/796,341	7 February 1997 (07.02.97)	US
08/796,339	7 February 1997 (07.02.97)	US
08/797,817	7 February 1997 (07.02.97)	US
08/796,335	7 February 1997 (07.02.97)	US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications

US	08/796,336 (CON)
Filed on	7 February 1997 (07.02.97)
US	08/796,340 (CON)
Filed on	7 February 1997 (07.02.97)
US	08/796,338 (CON)
Filed on	7 February 1997 (07.02.97)
US	08/797,813 (CON)
Filed on	7 February 1997 (07.02.97)
US	08/797,816 (CON)
Filed on	7 February 1997 (07.02.97)
US	08/797,820 (CON)
Filed on	7 February 1997 (07.02.97)
US	08/797,100 (CON)
Filed on	7 February 1997 (07.02.97)
US	08/796,337 (CON)
Filed on	7 February 1997 (07.02.97)
US	08/796,334 (CON)
Filed on	7 February 1997 (07.02.97)
US	08/796,341 (CON)
Filed on	7 February 1997 (07.02.97)
US	08/796,339 (CON)
Filed on	7 February 1997 (07.02.97)
US	08/797,817 (CON)
Filed on	7 February 1997 (07.02.97)
US	08/796,335 (CON)
Filed on	7 February 1997 (07.02.97)

(71) Applicant *(for all designated States except US)*: EMISPHERE TECHNOLOGIES, INC. [US/US]; 15 Skyline Drive, Hawthorne, NY 10532 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: LEONE-BAY, Andrea [US/US]; 20 Woodland Way, Ridgefield, CT 06877 (US). HO, Koc-Kan [-/US]; 104 Pheasant Run, Monmouth Junction, NJ 08852 (US). LEIPOLD, Harry, R. [US/US]; 63 Town Green Drive, Elmsford, NY 10523 (US). MILSTEIN, Sam, J. [US/US]; 15 Beechtree Lane, Larchmont, NY 10538 (US). SARRUBI, Donald, J. [US/US]; 18 Lawton Lane, Bronxville, NY 10708 (US). WANG, Eric [CN/US]; 1120 Warburton Avenue #1F, Yonkers, NY 10701 (US). GSCHNEIDNER, David [US/US]; 44 Cerretta Street #6, Stamford, CT 06907 (US).

(74) Agents: ROBINSON, Joseph, R. et al.; Darby & Darby P.C., 805 Third Avenue, New York, NY 10022 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: COMPOUNDS AND COMPOSITIONS FOR DELIVERING ACTIVE AGENTS

(57) Abstract

Carrier compounds and compositions which are useful in the delivery of active agents are provided. The carrier compound can be an amino acid derivative, and the active agent can be a peptide, mucopolysaccharide, carbohydrate, or lipid. Methods of administration, including oral administration, and preparation are provided as well.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

COMPOUNDS AND COMPOSITIONS FOR DELIVERING ACTIVE AGENTS

FIELD OF THE INVENTION

The present invention relates to compounds for delivering active agents, and particularly biologically or chemically active agents. These compounds are used as carriers to facilitate the delivery of a cargo to a target. The carrier compounds are well suited to form non-covalent mixtures with biologically-active agents for oral administration to animals. Methods for the preparation administration of such compositions are also disclosed.

BACKGROUND OF THE INVENTION

Conventional means for delivering active agents are often severely limited by biological, chemical, and physical barriers. Typically, these barriers are imposed by the environment through which delivery occurs, the environment of the target for delivery, or the target itself. Biologically or chemically active agents are particularly vulnerable to such barriers.

For example in the delivery to animals of biologically active or chemically active pharmacological and therapeutic agents, barriers are imposed by the body. Examples of physical barriers are the skin and various organ membranes

that must be traversed before reaching a target. Chemical barriers include, but are not limited to, pH variations, lipid bi-layers, and degrading enzymes.

These barriers are of particular significance in the design of oral delivery systems. Oral delivery of many biologically or chemically active agents would be the route of choice for administration to animals if not for biological, chemical, and physical barriers such as varying pH in the gastro-intestinal (GI) tract, powerful digestive enzymes, and active agent impermeable gastro-intestinal membranes. Among the numerous agents which are not typically amenable to oral administration are biologically or chemically active peptides, such as calcitonin and insulin; polysaccharides, and in particular mucopolysaccharides including, but not limited to, heparin; heparinoids; antibiotics; and other organic substances. These agents are rapidly rendered ineffective or are destroyed in the gastro-intestinal tract by acid hydrolysis, enzymes, or the like.

Earlier methods for orally administering vulnerable pharmacological agents have relied on the co-administration of adjuvants (e.g., resorcinols and non-ionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether) to increase artificially the permeability of the intestinal walls, as well as the co-administration of enzymatic inhibitors (e.g., pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF) and trasylol) to inhibit enzymatic degradation.

Liposomes have also been described as drug delivery systems for insulin and heparin. See, for example, U.S. Patent No. 4,239,754; Patel et al. (1976), *FEBS Letters*, Vol. 62, pg. 60; and Hashimoto et al. (1979), *Endocrinology Japan*, Vol. 26, pg. 337.

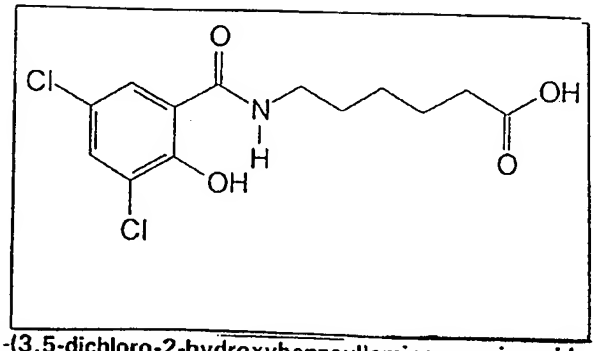
However, broad spectrum use of such drug delivery systems is precluded because: (1) the systems require toxic amounts of adjuvants or inhibitors; (2) suitable low molecular weight cargos, i.e. active agents, are not available; (3) the systems exhibit poor stability and inadequate shelf life; (4) the systems are difficult to manufacture; (5) the systems fail to protect the active agent (cargo); (6) the systems adversely alter the active agent; or (7) the systems fail to allow or promote absorption of the active agent.

More recently, microspheres of artificial polymers of mixed amino acids (proteinoids) have been used to deliver pharmaceuticals. For example, U.S. Patent No. 4,925,673 describes drug-containing proteinoid microsphere carriers as well as methods for their preparation and use. These proteinoid microspheres are useful for the delivery of a number of active agents.

There is still a need in the art for simple, inexpensive delivery systems which are easily prepared and which can deliver a broad range of active agents.

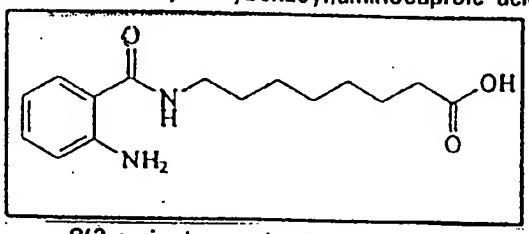
SUMMARY OF THE INVENTION

Compounds and compositions which are useful in the delivery of active agents are provided. These compositions include at least one active agent, preferably a biologically or chemically active agent, and at least one of the following compounds 1-193, or salts thereof.



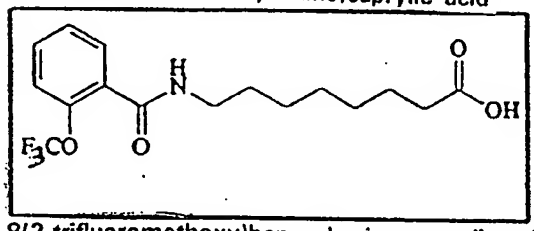
1

6-N-(3,5-dichloro-2-hydroxybenzoyl)aminocaproic acid



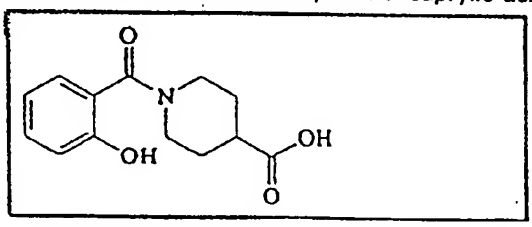
2

8(2-aminobenzoylamino)caprylic acid



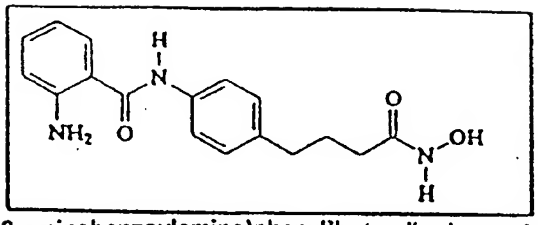
3

8(2-trifluoromethoxy)benzoylamino caprylic acid



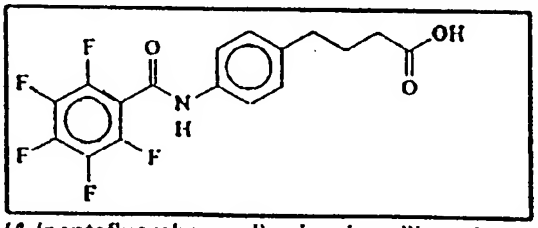
4

N-(2-hydroxybenzoyl)isonipecotic acid



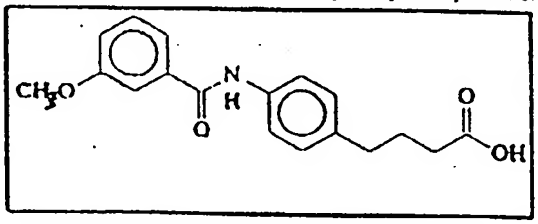
5

4-[4-(2-aminobenzoylamino)phenyl]butyrylhydroxamic acid



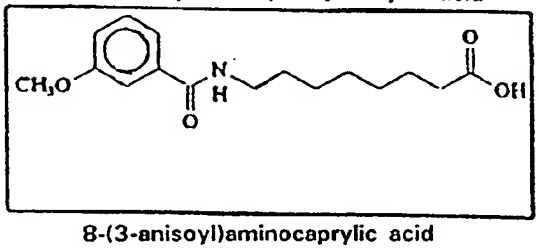
6

4-(4-(pentafluorobenzoyl)aminophenyl)butyric acid



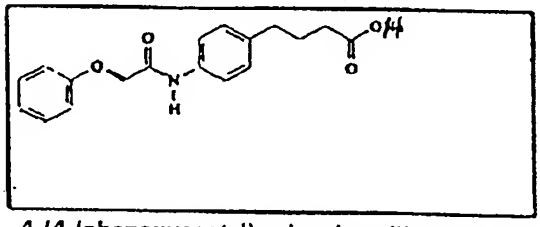
7

4-(4-(3-anisoyl)aminophenyl)butyric acid



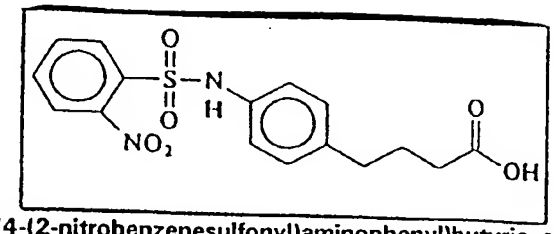
8

8-(3-anisoyl)aminocaprylic acid



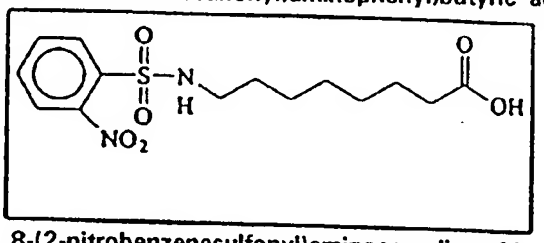
9

4-(4-(phenoxyacetyl)aminophenyl)butyric acid



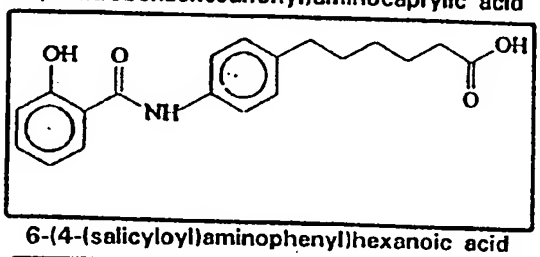
10

4-(4-(2-nitrobenzenesulfonyl)aminophenyl)butyric acid



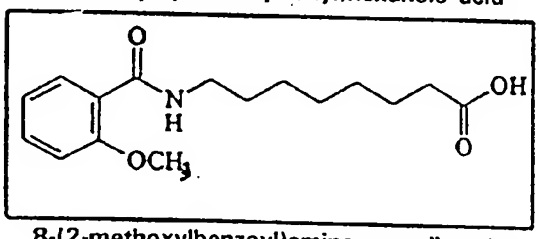
11

8-(2-nitrobenzenesulfonyl)aminocaprylic acid



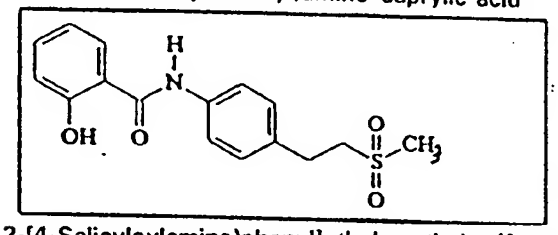
12

6-(4-(salicyloyl)aminophenyl)hexanoic acid



13

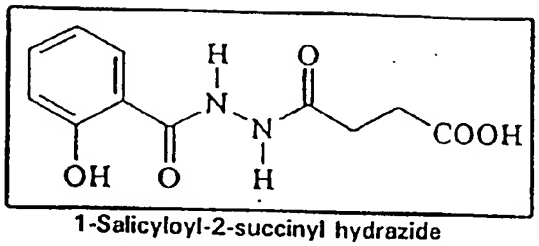
8-(2-methoxylbenzoyl)amino caprylic acid



14

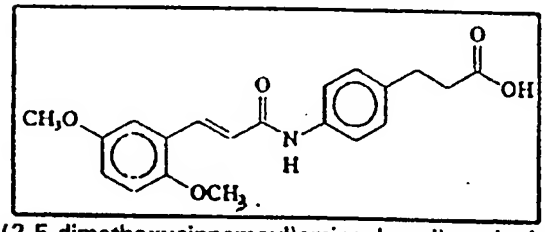
2-(4-Salicyloylamino)phenyl]ethyl methyl sulfone

15



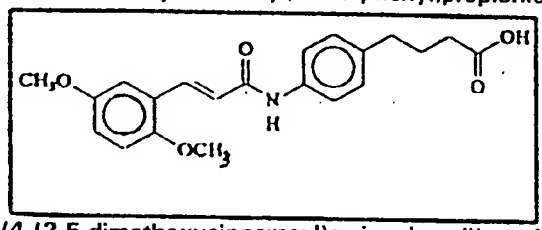
1-Salicyloyl-2-succinyl hydrazide

16



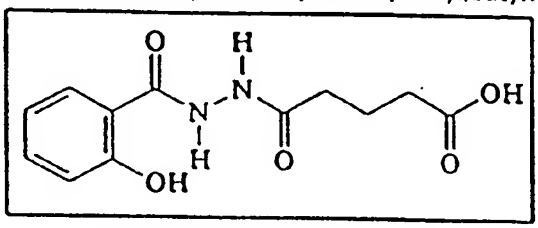
3-(4-(2,5-dimethoxycinnamoyl)aminophenyl)propionic acid

17

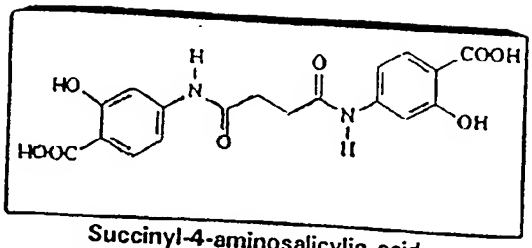


4-(4-(2,5-dimethoxycinnamoyl)aminophenyl)butyric acid

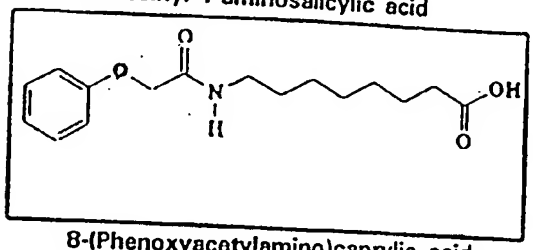
18



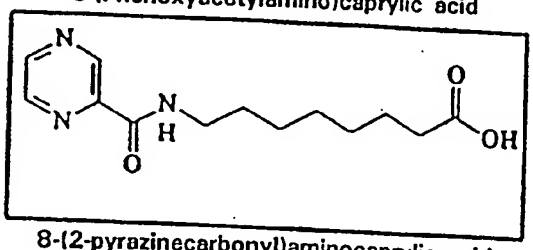
1-salicyloyl-2-glutaryl hydrazide



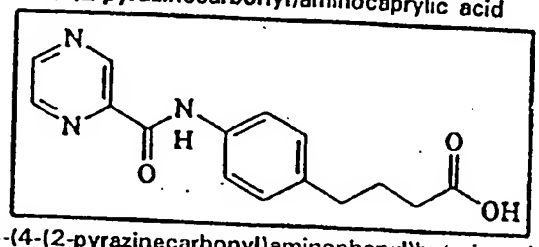
Succinyl-4-aminosalicylic acid 19



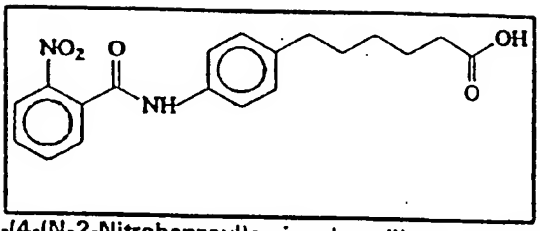
8-(Phenoxyacetylamino)caprylic acid 20



8-(2-pyrazinecarbonyl)aminocaprylic acid 21

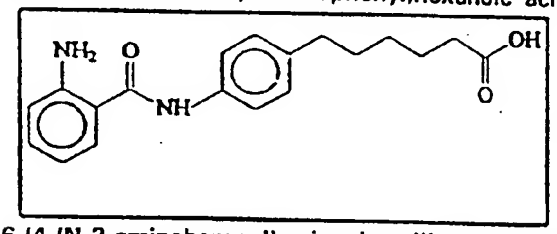


4-(4-(2-pyrazinecarbonyl)aminophenyl)butyric acid 22



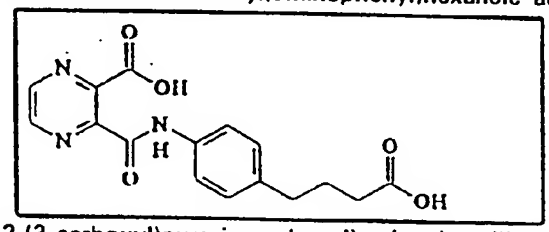
23

6-(4-(N-2-Nitrobenzoyl)aminophenyl)hexanoic acid



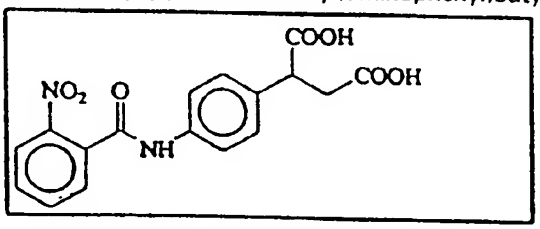
24

6-(4-(N-2-aminobenzoyl)aminophenyl)hexanoic acid



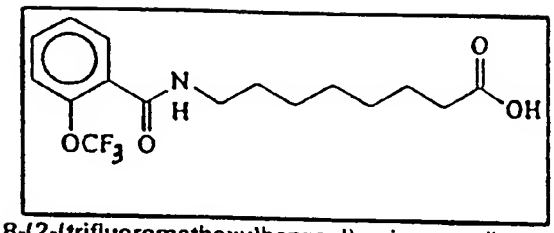
25

4-(4-(2-(3-carboxyl)pyrazinecarboxyl)aminophenyl)butyric acid



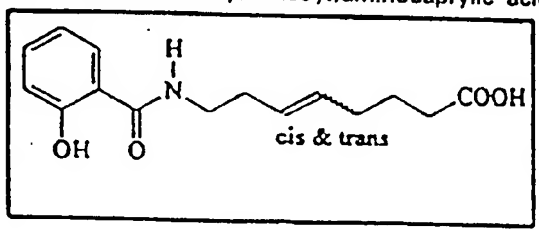
26

4(2-Nitrobenzoyl)aminophenylsuccinic acid

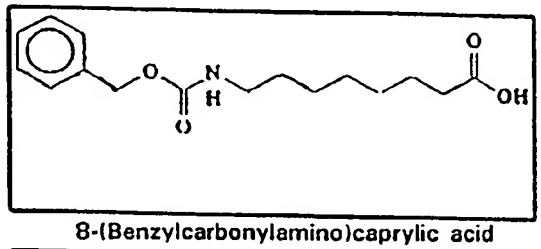


27

8-(2-(trifluoromethoxy)benzoyl)aminocaprylic acid

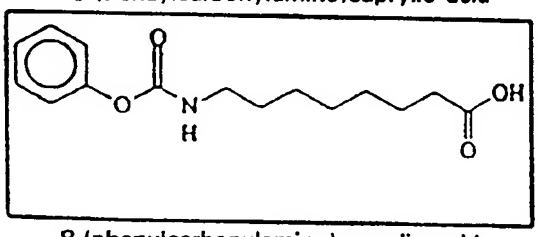


28



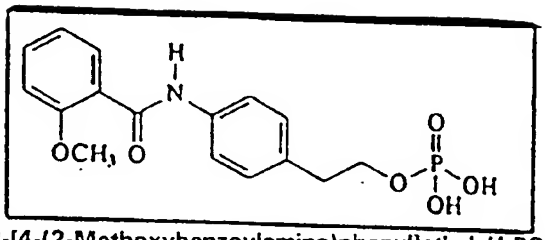
29

8-(Benzylcarbonylamino)caprylic acid

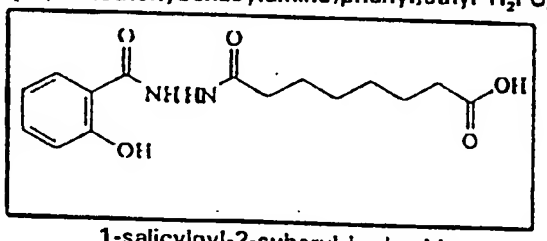


30

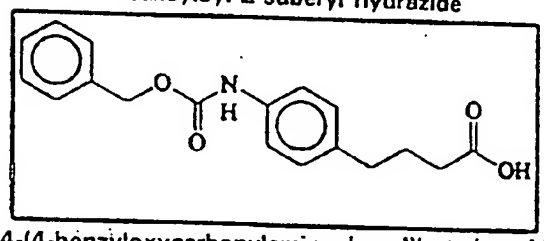
8-(phenylcarbonylamino)caprylic acid



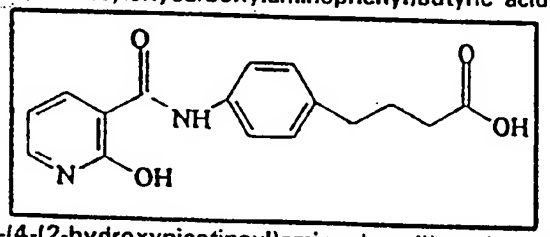
2-[4-(2-Methoxybenzoylamino)phenyl]ethyl H_2PO_4 31



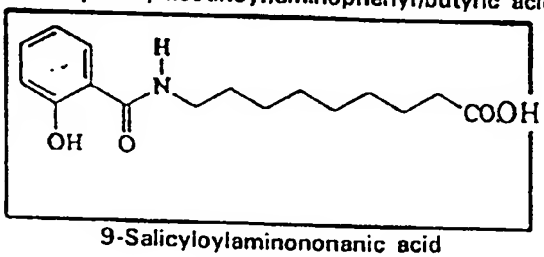
1-salicyloyl-2-suberyl hydrazide 32



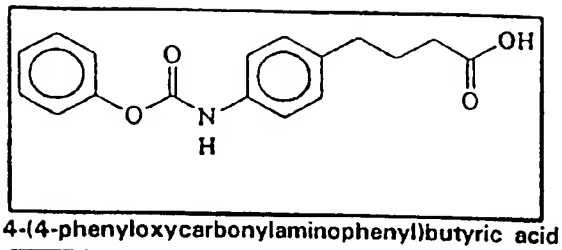
4-(4-benzyloxycarbonylaminophenyl)butyric acid 33



4-(4-(2-hydroxynicotinoyl)aminophenyl)butyric acid 34

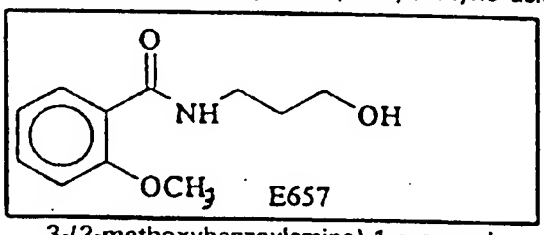


9-Salicyloylaminononanic acid 35



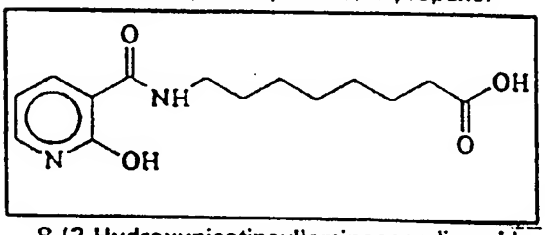
36

4-(4-phenyloxycarbonylaminophenyl)butyric acid



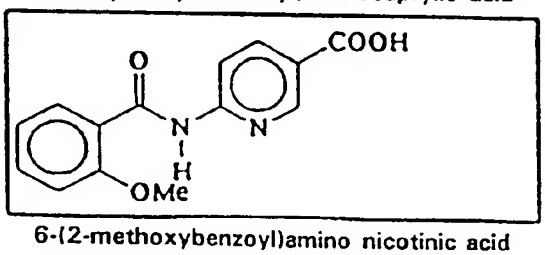
37

3-(2-methoxybenzoylamino)-1-propanol



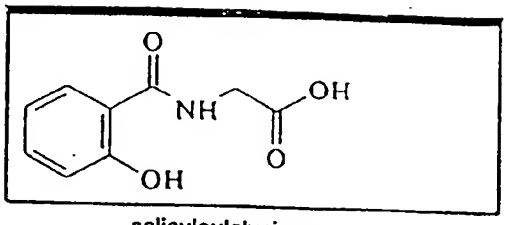
38

8-(2-Hydroxynicotinoyl)aminocaprylic acid



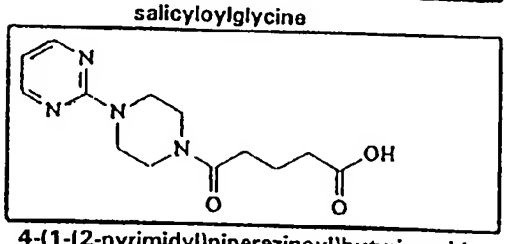
39

6-(2-methoxybenzoyl)amino nicotinic acid



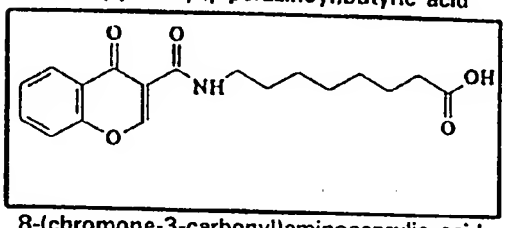
salicyloylglycine

40



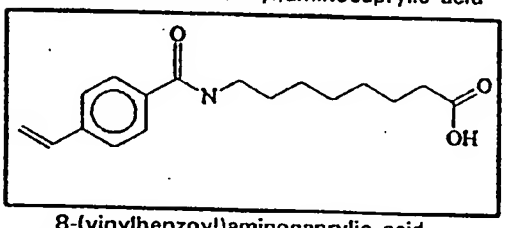
4-(1-(2-pyrimidyl)piperazinoyl)butyric acid

41



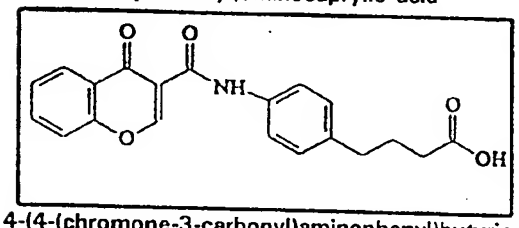
8-(chromone-3-carbonyl)aminocaprylic acid

42



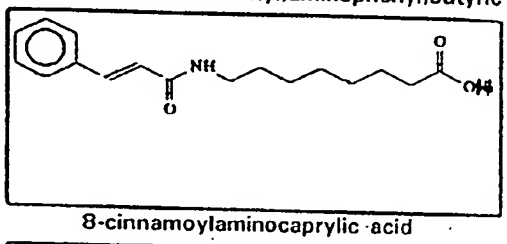
8-(vinylbenzoyl)aminocaprylic acid

43



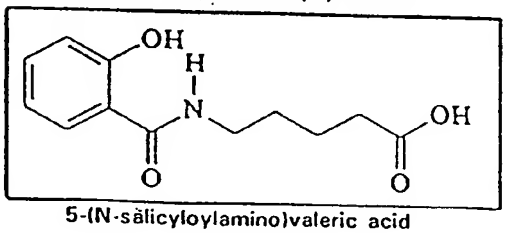
4-(4-(chromone-3-carbonyl)aminophenyl)butyric acid

44



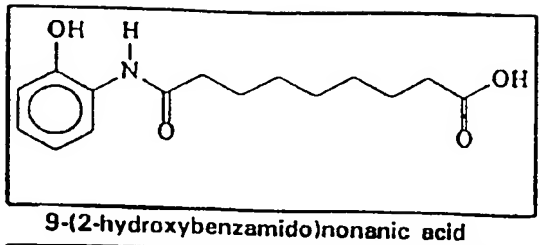
8-cinnamoylaminocaprylic acid

45



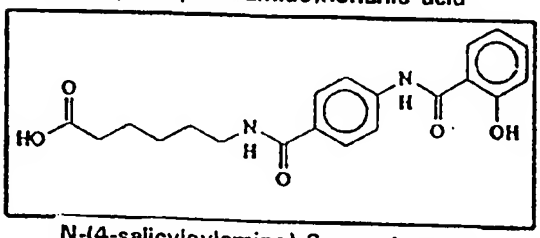
5-(N-salicyloylamino)valeric acid

46



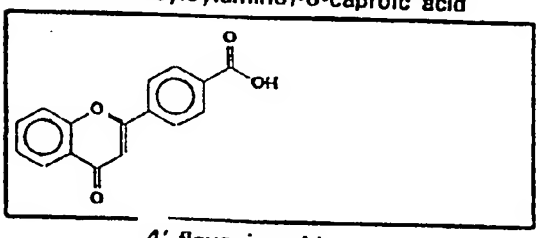
47

9-(2-hydroxybenzamido)nonanic acid



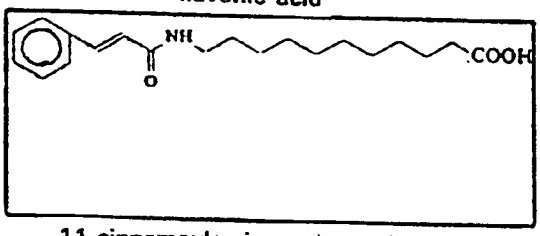
48

N-(4-salicyloylamino)-6-caproic acid



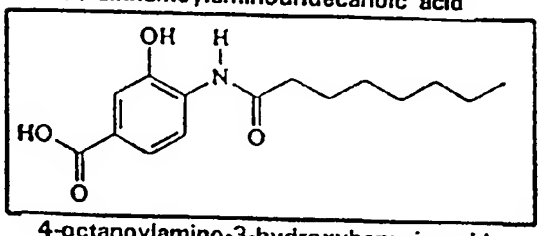
49

4'-flavonic acid



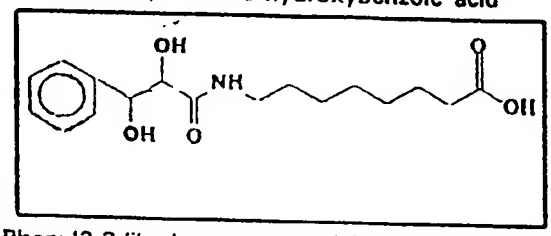
50

11-cinnamoylaminoundecanoic acid



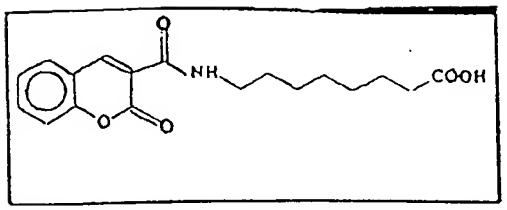
51

4-octanoylamino-3-hydroxybenzoic acid



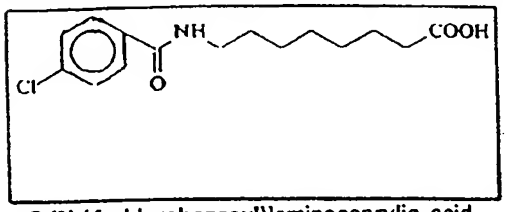
52

(3Phenyl2,3dihydroxypropanoyl)8aminocaprylic acid



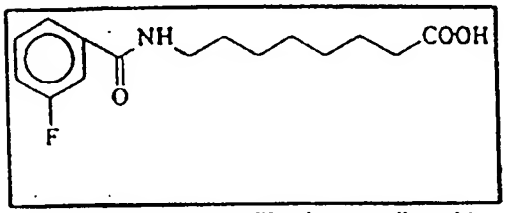
8-[N-(3-coumarincarbonyl)]aminocaprylic acid

53



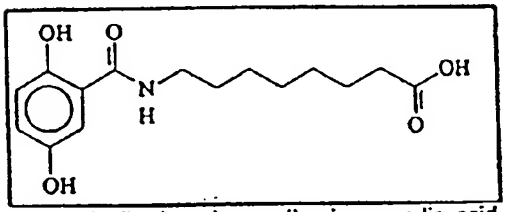
8-[N-(4-chlorobenzoyl)]aminocaprylic acid

54



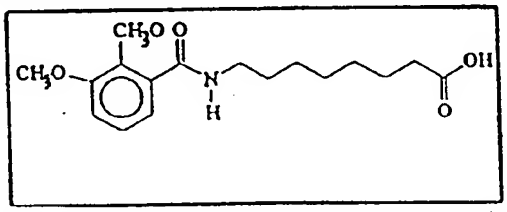
8-[N-3-fluorobenzoyl)]aminocaprylic acid

55



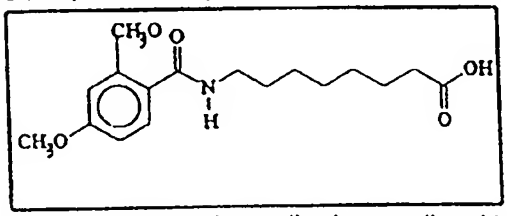
8-(N-2,5-Dihydroxybenzoyl)aminocaprylic acid

56



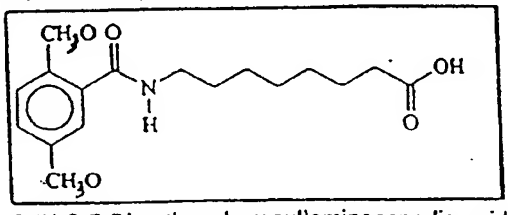
8-(N-2,3-Dimethoxybenzoyl)aminocaprylic acid

57



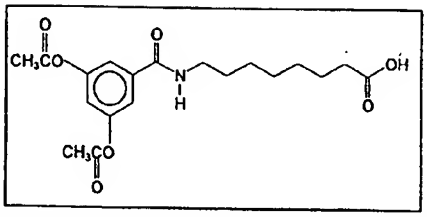
8-(N-2,4-Dihydroxybenzoyl)aminocaprylic acid

58



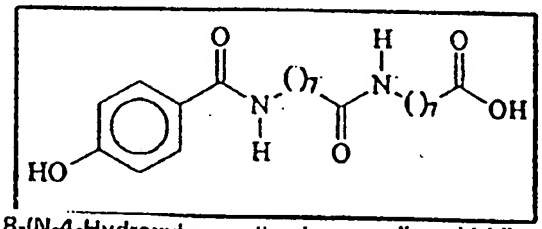
8-(N-2,5-Dimethoxybenzoyl)aminocaprylic acid

59



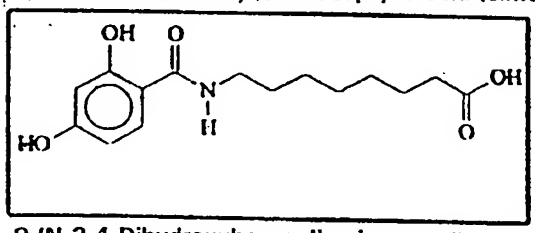
60

8-(N-3,5-Diacetyloxybenzoyl)aminocaprylic acid



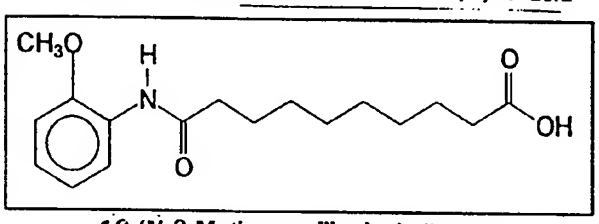
61

8-(N-4-Hydroxybenzoyl)aminocaprylic acid (dimer)



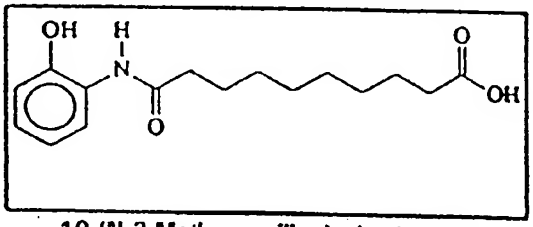
62

8-(N-2,4-Dihydroxybenzoyl)aminocaprylic acid



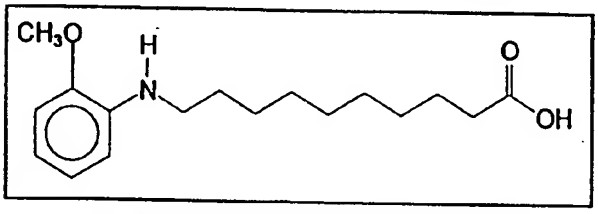
63

10-(N-2-Methoxyanilino)sebalic acid



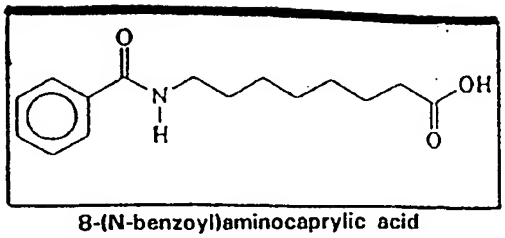
64

10-(N-2-Methoxyanilino)sebacic acid



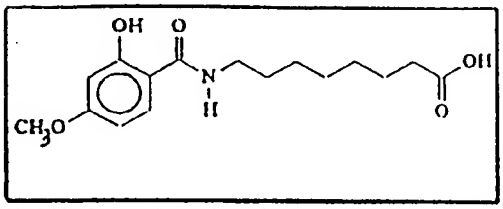
65

2-Methoxybenzenaminodecanoic acid



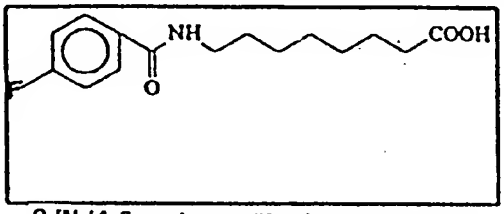
66

8-(N-benzoyl)aminocaprylic acid



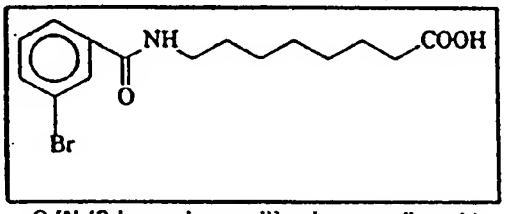
67

8-(N-2-Hydroxy-4-methoxybenzoyl)aminocaprylic acid



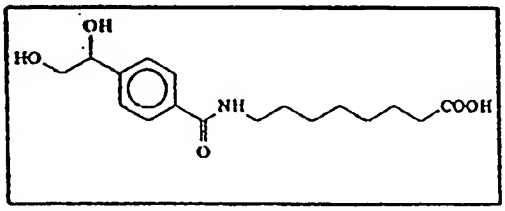
68

8-[N-(4-fluorobenzoyl)]aminocaprylic acid



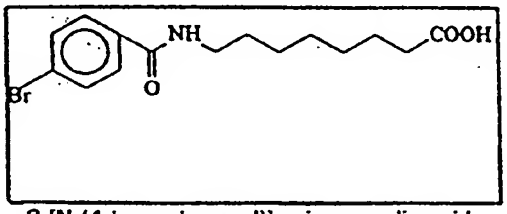
69

8-[N-(3-bromobenzoyl)]aminocaprylic acid



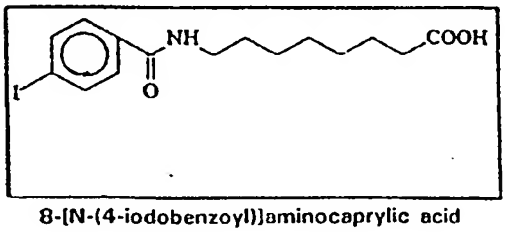
70

8-(4-(1,2-dihydroxyethyl)benzoyl)aminocaprylic acid



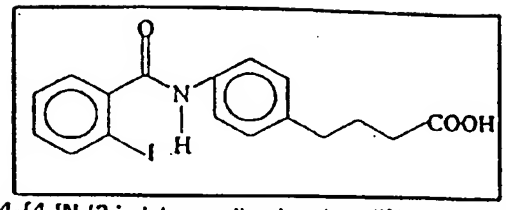
71

8-[N-(4-bromobenzoyl)]aminocaprylic acid



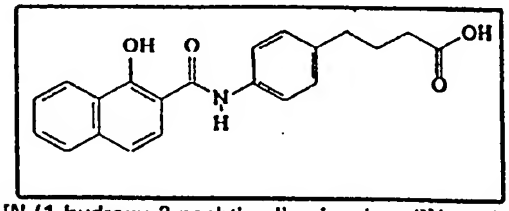
72

8-[N-(4-iodobenzoyl)]aminocaprylic acid



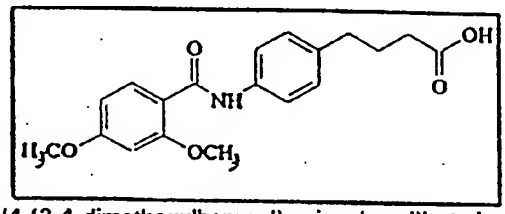
73

4-{4-[N-(2-iodobenzoyl)aminophenyl]}butyric acid



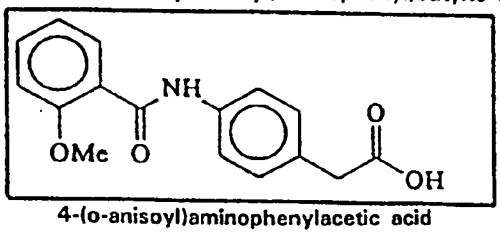
74

4-{4-[N-(1-hydroxy-2-naphthoyl)aminophenyl]}butyric acid



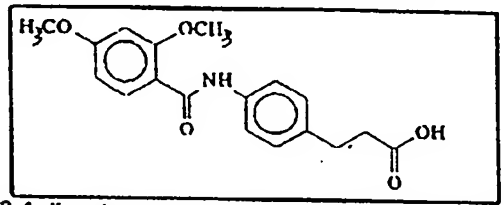
75

4-(4-(2,4-dimethoxylbenzoyl)aminophenyl)butyric acid



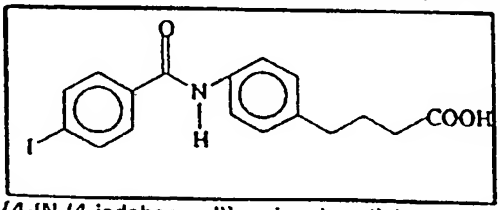
76

4-(o-anisoyl)aminophenylacetic acid



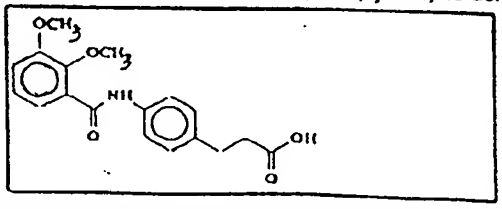
77

3-[4-(2,4-dimethoxybenzoyl) aminophenyl] propionic acid



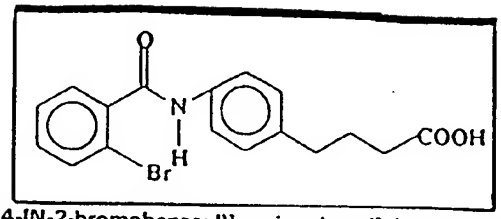
78

4-{4-[N-(4-iodobenzoyl)] aminophenyl} butyric acid



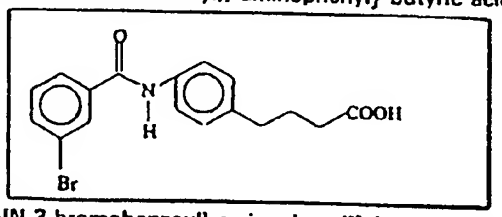
79

3-[4-(2,3-dimethoxybenzoyl) aminophenyl] propionic acid



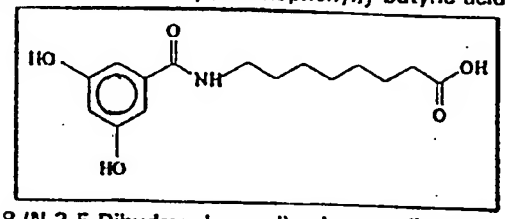
80

4{4-[N-2-bromobenzoyl)] aminophenyl} butyric acid



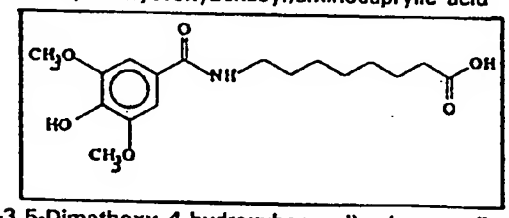
81

4{4-[N-3-bromobenzoyl) aminophenyl]} butyric acid



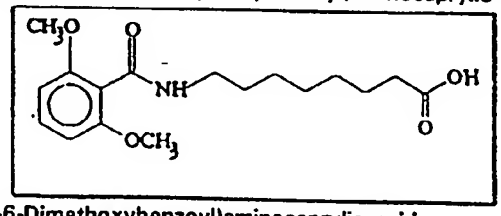
82

8-(N-3,5 Dihydroxybenzoyl)aminocaprylic acid



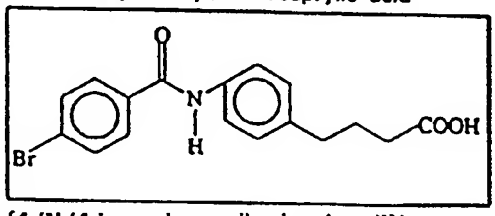
83

8-(N-3,5-Dimethoxy 4-hydroxybenzoyl)aminocaprylic acid



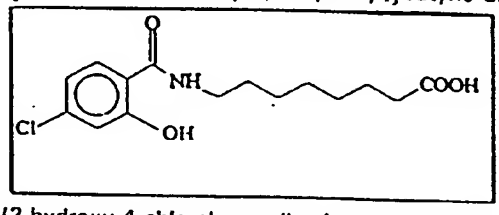
84

8-(N-2-6-Dimethoxybenzoyl)aminocaprylic acid



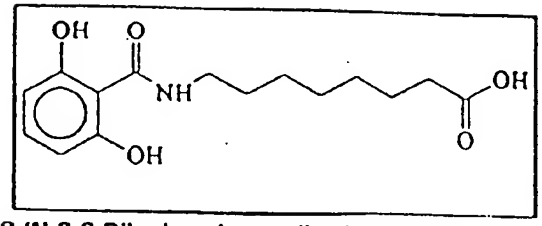
85

4-{4-[N-(4-bromobenzoyl)aminophenyl]}butyric acid



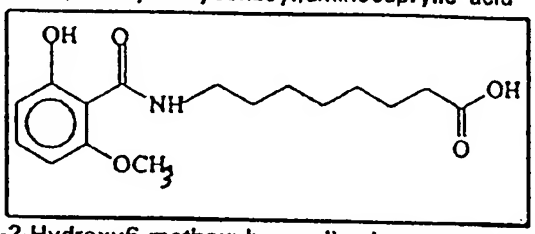
86

8-(2-hydroxy-4-chlorobenzoyl)aminocaprylic acid



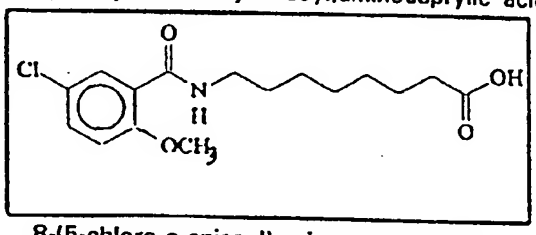
87

8-(N-2,6-Dihydroxybenzoyl)aminocaprylic acid



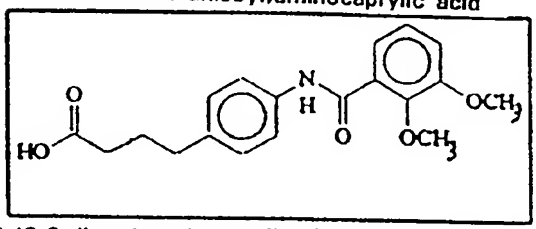
88

8-(N-2-Hydroxy6-methoxybenzoyl)aminocaprylic acid



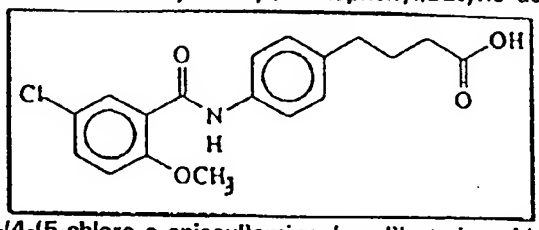
89

8-(5-chloro-o-anisoyl)aminocaprylic acid



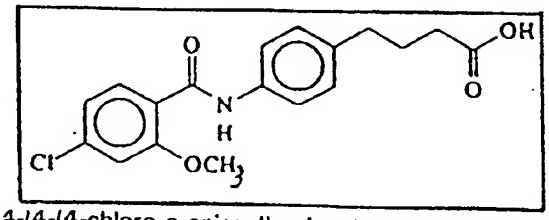
90

4-(4-(2,3-dimethoxybenzoyl)aminophenyl)butyric acid



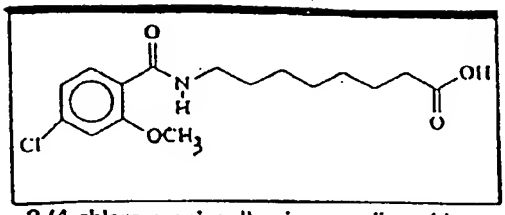
91

4-(4-(5-chloro-o-anisoyl)aminophenyl)butyric acid



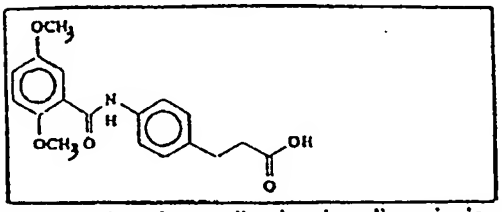
92

4-(4-(4-chloro-o-anisoyl)aminophenyl)butyric acid



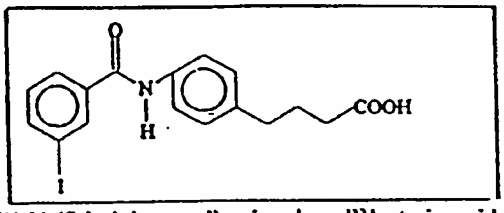
93

8-(4-chloro-o-anisoyl)aminocaprylic acid



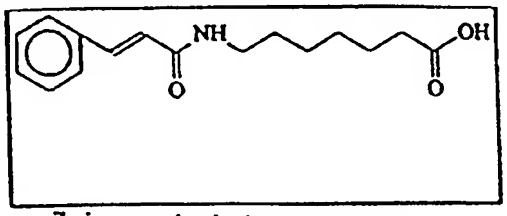
94

3-(4-(2,5-dimethoxybenzoyl)aminophenyl)propionic acid



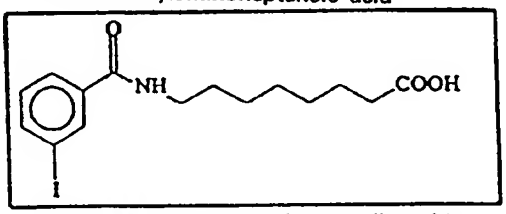
95

4-{N-[4-(3-iodobenzoyl)aminophenyl]}butyric acid



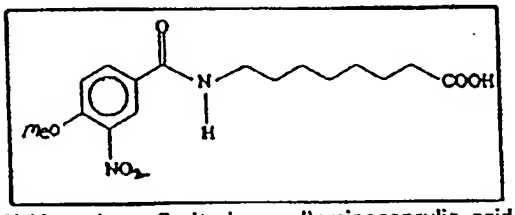
96

7-cinnamoylaminoheptanoic acid



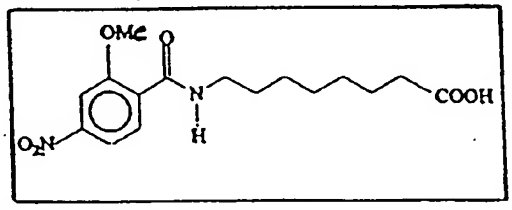
97

8-N-(3-iodobenzoyl)aminocaprylic acid



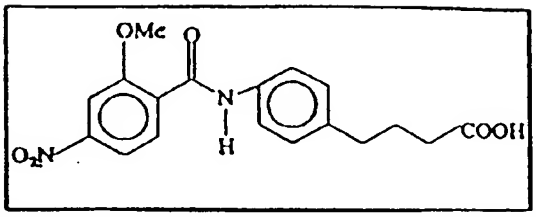
98

8-N-(4-methoxy-3-nitrobenzoyl)aminocaprylic acid



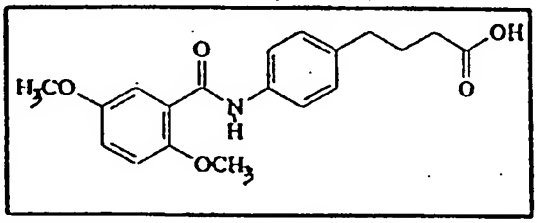
99

8-N-(2-methoxy-4-nitrobenzoyl)aminocaprylic acid



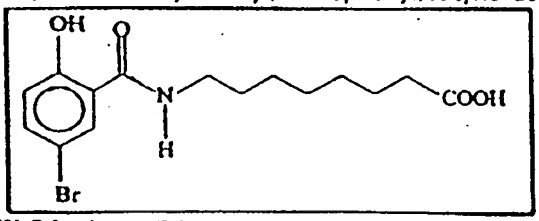
100

4-{N-[4-(2-methoxy-4-nitrobenzoyl)aminophenyl]}butyric acid



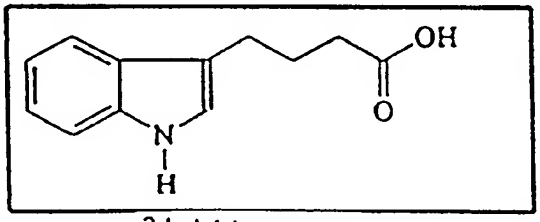
101

4-(4-(2,5-dimethoxybenzoyl)aminophenyl)butyric acid



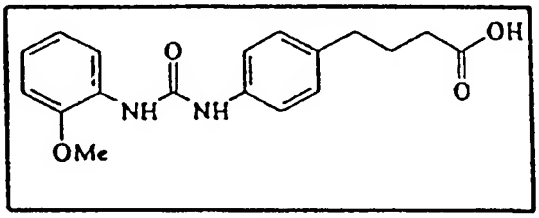
102

8-(N-2-hydroxy-5-bromobenzoyl)aminocaprylic acid

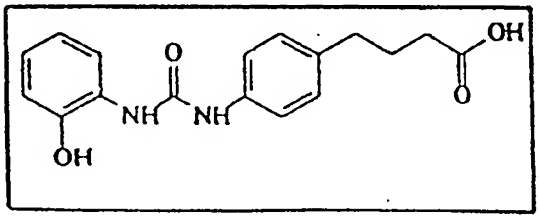


103

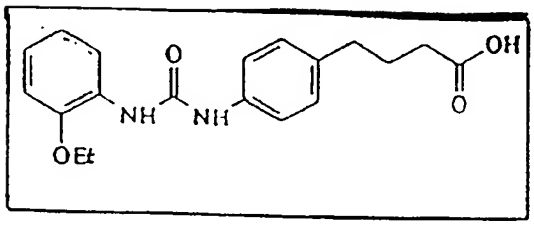
3-Indolebutyric acid



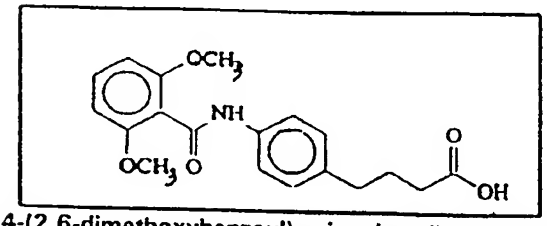
104



105

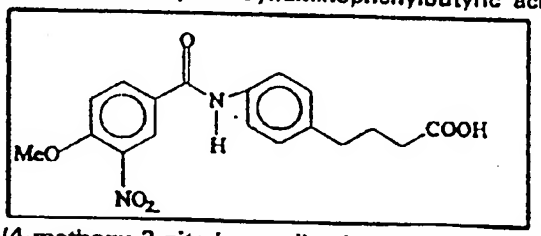


106



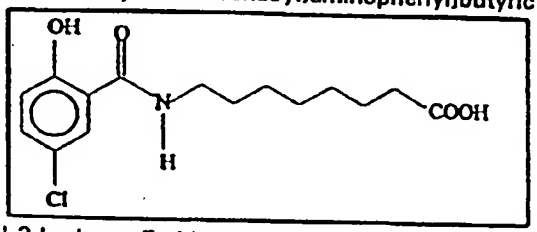
107

4-(4-(2,6-dimethoxybenzoyl)aminophenylbutyric acid



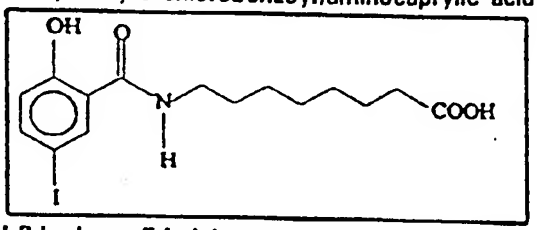
108

4-[4-N-(4-methoxy-3-nitrobenzoyl)aminophenyl]butyric acid



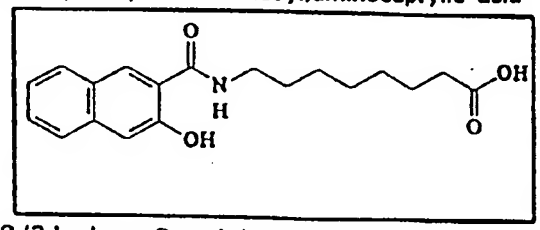
109

8-(N-2-hydroxy-5-chlorobenzoyl)aminocaprylic acid



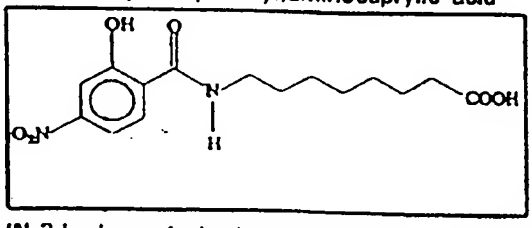
110

8-(N-2-hydroxy-5-iodobenzoyl)aminocaprylic acid



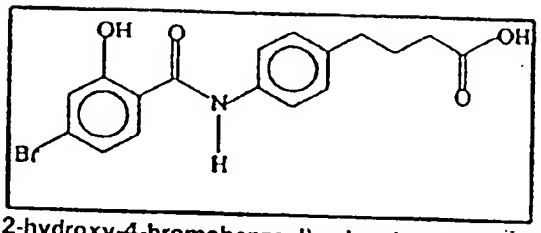
111

8-(3-hydroxy-2-naphthoyl)aminocaprylic acid



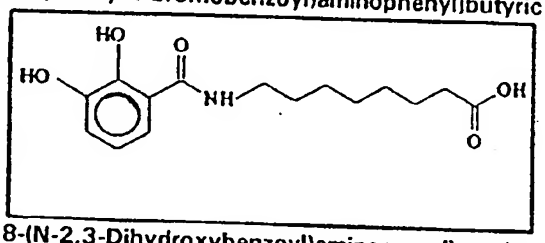
112

8-(N-2-hydroxy-4-nitrobenzoyl)aminocaprylic acid



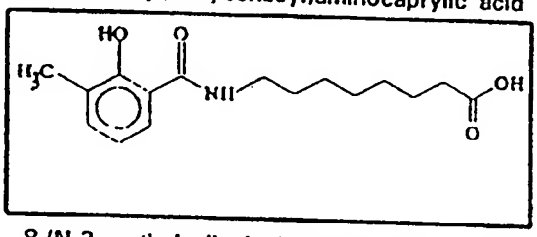
113

4-[-N-(2-hydroxy-4-bromobenzoyl)aminophenyl]butyric acid



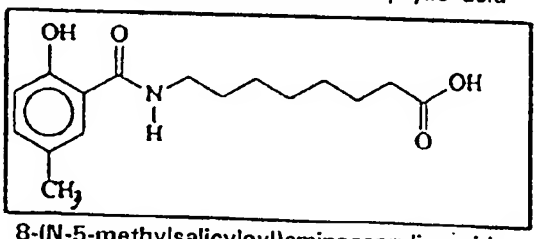
114

8-(N-2,3-Dihydroxybenzoyl)aminocaprylic acid



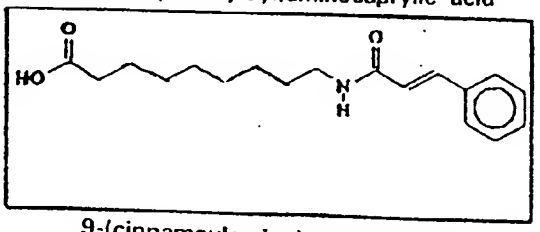
115

8-(N-3-methylsalicyloyl)aminocaprylic acid



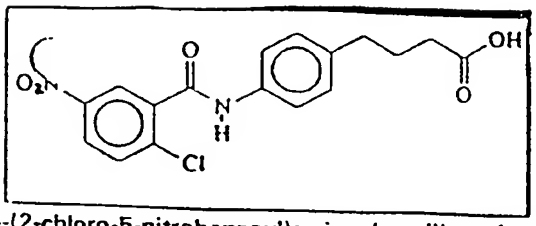
116

8-(N-5-methylsalicyloyl)aminocaprylic acid



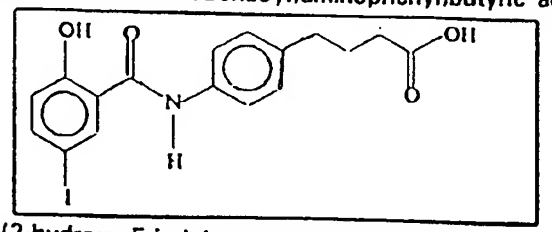
117

9-(cinnamoylamino)nonanoic acid



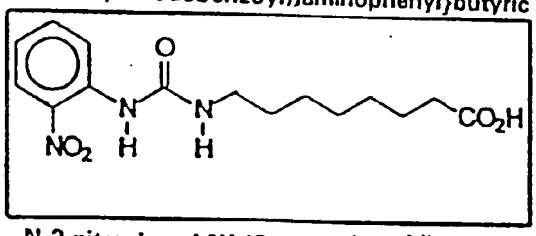
118

4-(4-(2-chloro-5-nitrobenzoyl)aminophenyl)butyric acid



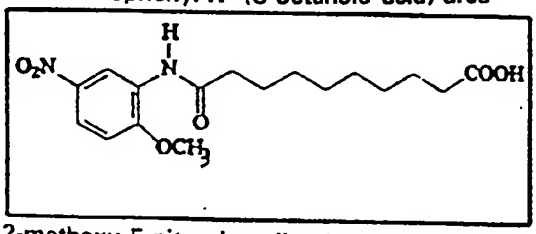
119

4-{-[N-(2-hydroxy-5-iodobenzoyl)]aminophenyl}butyric acid



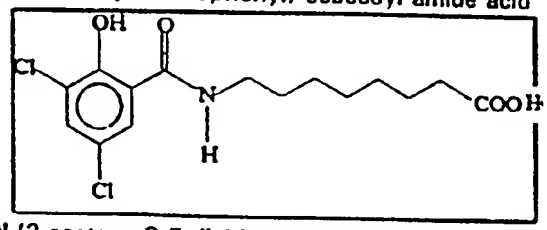
120

N-2-nitrophenyl-N'-(8-octanoic acid) urea



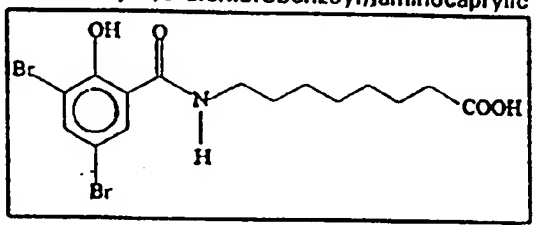
121

N-(2-methoxy-5-nitrophenyl) sebecoyl amide acid



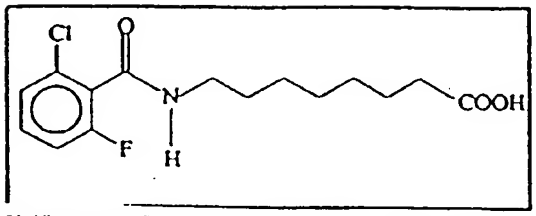
122

8-[N-(2-acetoxy-3,5-dichlorobenzoyl)]aminocaprylic acid



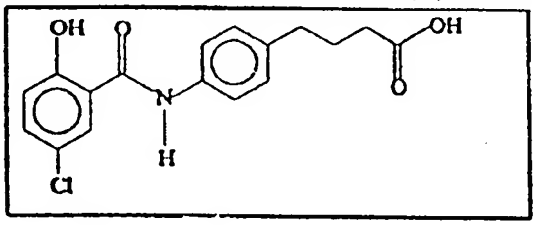
123

8-[N-(2-acetoxy-3,5-dibromobenzoyl)]aminocaprylic acid

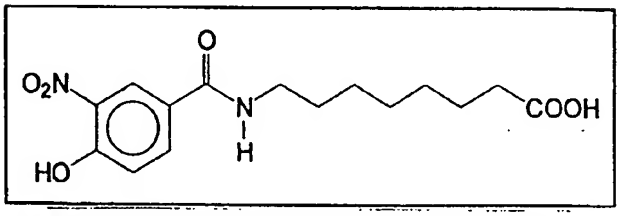


124

8-N-(2-chloro-6-fluorobenzoyl)aminocaprylic acid

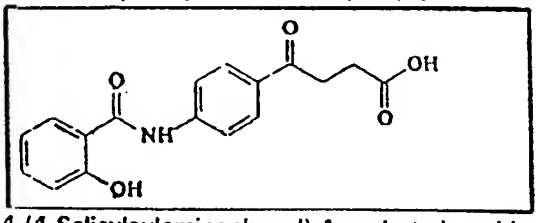


125



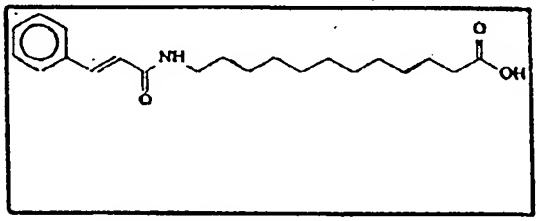
126

8-N-(4-hydroxy-3-nitrobenzoyl)caprylic acid



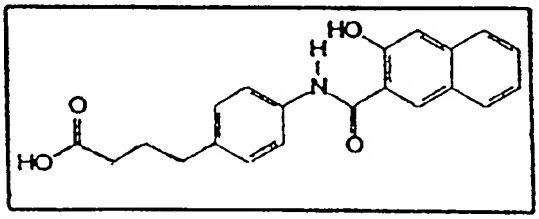
127

4-(4-Salicyloylaminophenyl)-4-oxobutyric acid



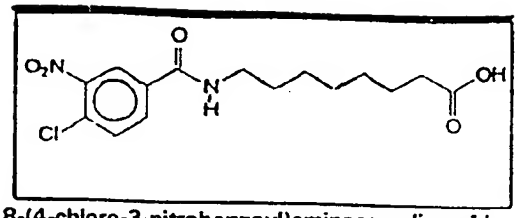
128

12-cinnamoyldodecanoic acid



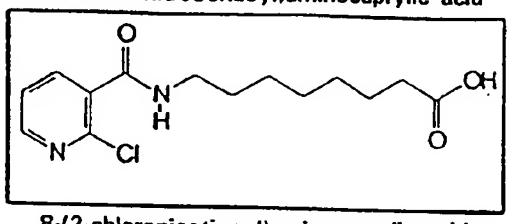
129

4-{4-[N-(3-hydroxy-2-napthoyl)aminophenyl]}butyric acid



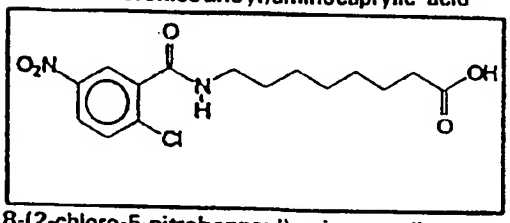
130

8-(4-chloro-3-nitrobenzoyl)aminocaprylic acid



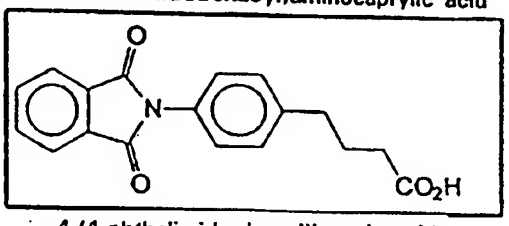
131

8-(2-chloronicotinoyl)aminocaprylic acid



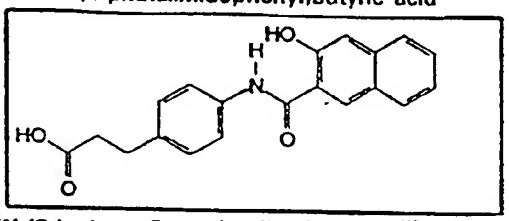
132

8-(2-chloro-5-nitrobenzoyl)aminocaprylic acid



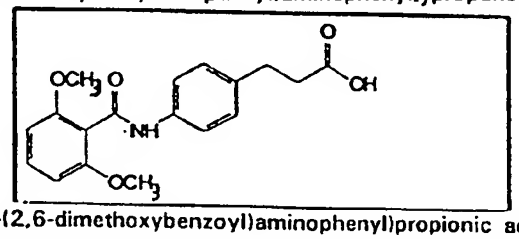
133

4-(4-phthalimidophenyl)butyric acid



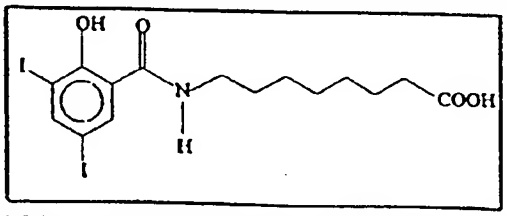
134

4-{4-[N-(3-hydroxy-2-napthoyl)aminophenyl]}propanoic acid



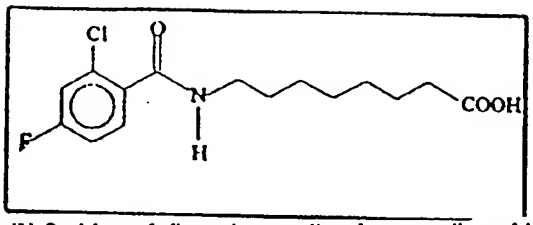
135

3-(4-(2,6-dimethoxybenzoyl)aminophenyl)propionic acid



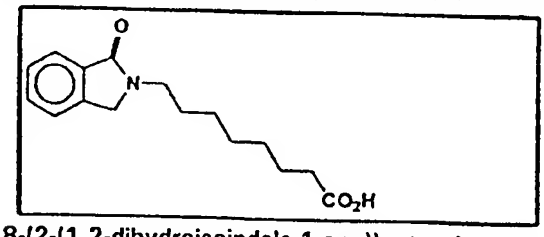
136

8-(N-2-hydroxy-3,5-diiodobenzoyl)aminocaprylic acid



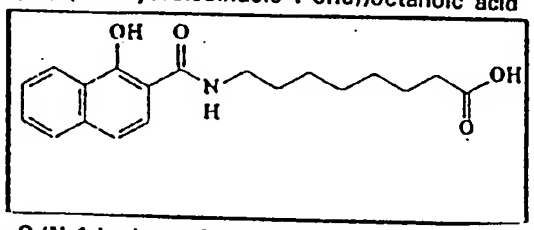
137

8-(N-2-chloro-4-fluorobenzoyl)aminocaprylic acid



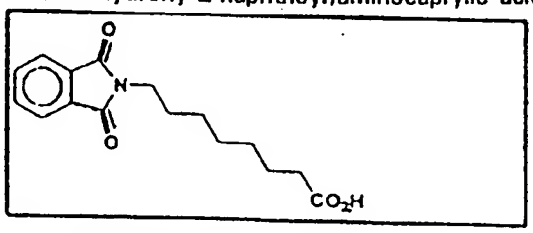
138

8-(2-(1,2-dihydroisoindole-1-one))octanoic acid



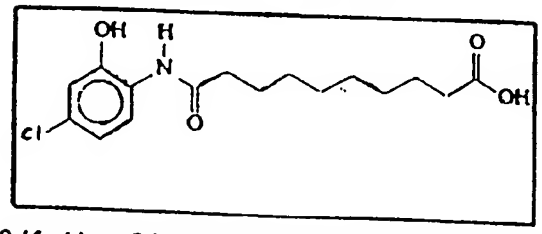
139

8-(N-1-hydroxy-2-naphthoyl)aminocaprylic acid



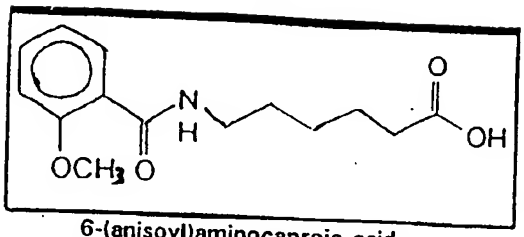
140

8-(phthalimido)caprylic acid



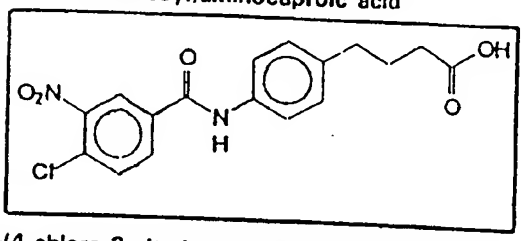
141

10-(4-chloro-2-hydroxyanilino)sebacic acid monoamide



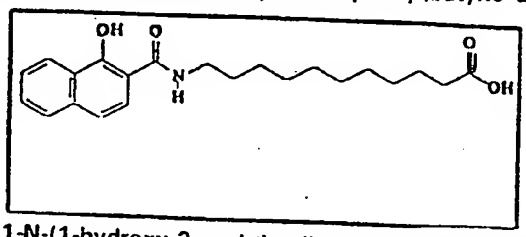
142

6-(anisoyl)aminocaproic acid



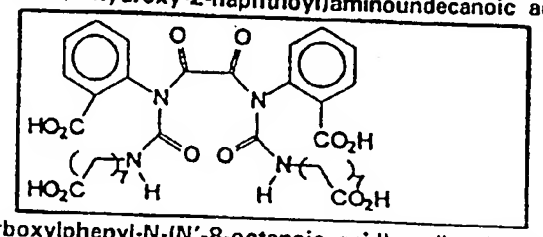
143

4-(4-(4-chloro-3-nitrobenzoyl)aminophenyl)butyric acid



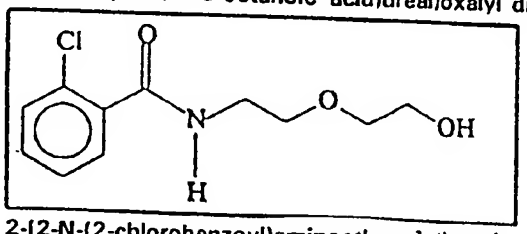
144

11-N-(1-hydroxy-2-naphthoyl)aminoundecanoic acid



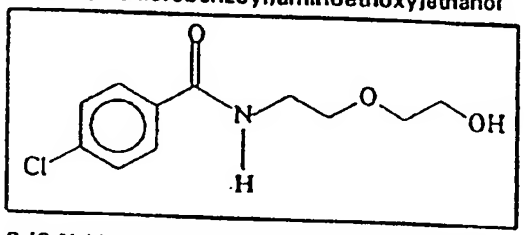
145

Bis(N-2carboxylphenyl-N-(N'-8-octanoic acid)ureal)oxalyl diamide



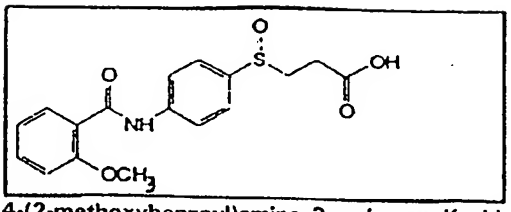
146

2-[2-N-(2-chlorobenzoyl)aminoethoxy]ethanol



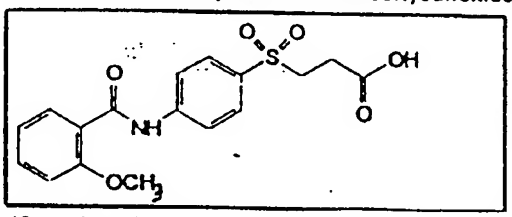
147

2-[2-N-(4-chlorobenzoyl)aminoethoxy]ethanol



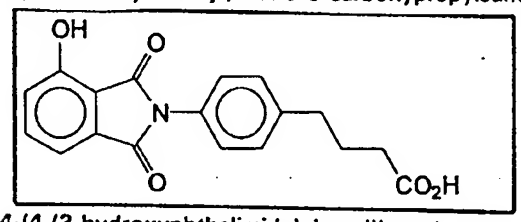
148

4-(2-methoxybenzoyl)amino 3-carboxysulfoxide



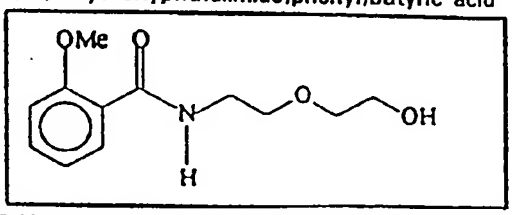
149

4-(2-methoxybenzoyl)amino 3-carboxypropylsulfone



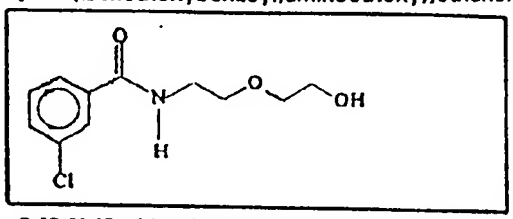
150

4-(4-(3-hydroxyphthalimido)phenyl)butyric acid



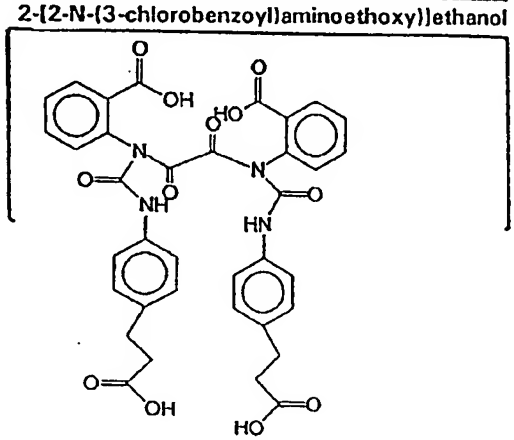
151

2-[2-N-(2-methoxybenzoyl)aminoethoxy)]ethanol



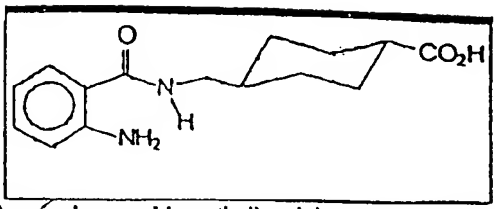
152

2-[2-N-(3-chlorobenzoyl)aminoethoxy)]ethanol



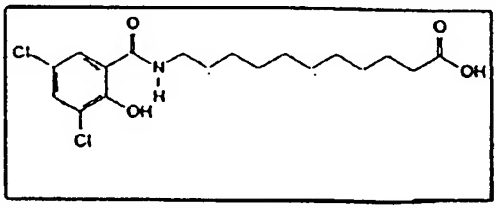
153

Bis(N-2-carboxyphenyl-N-(N'-3(4-aminophenyl)propionic acid)ureal)oxaylyl diamide



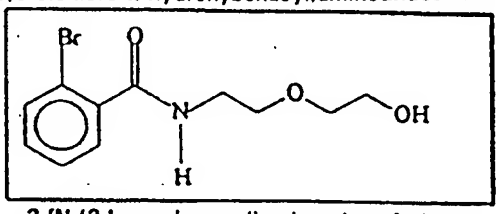
154

trans-4-(2-aminobenzamidomethyl)cyclohexamecarboxylic acid



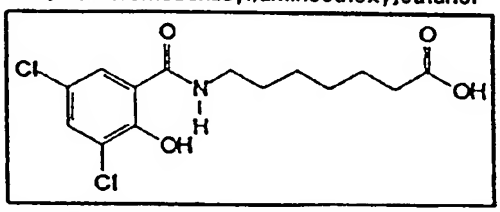
155

11-N-(3,5-dichloro-2-hydroxybenzoyl)aminoundecanoic acid



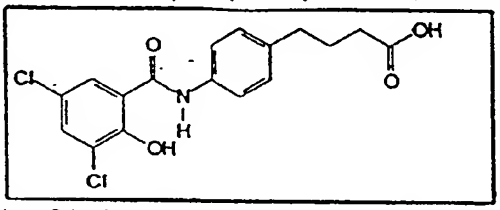
156

2-[N-(2-bromobenzoyl)aminoethoxy]ethanol



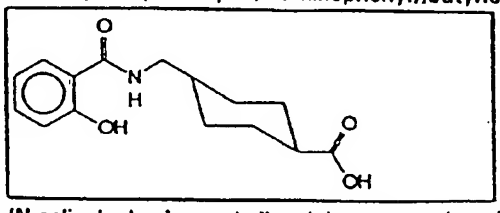
157

7-N-(3,5-dichloro-2-hydroxybenzoyl)aminoheptanoic acid



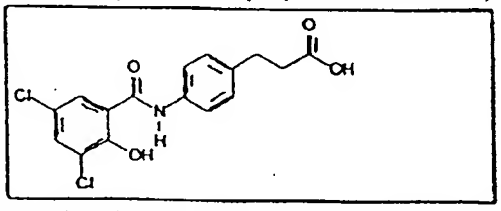
158

N-[3,5-dichloro-2-hydroxybenzoyl-4(4-aminophenyl)]butyric acid



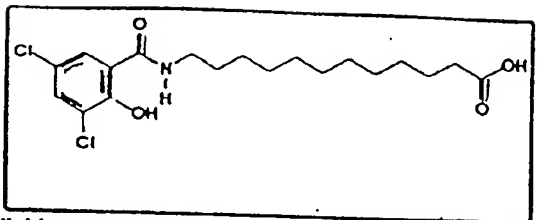
159

trans-4-(N-salicyloylaminomethyl)cyclohexane carboxylic acid



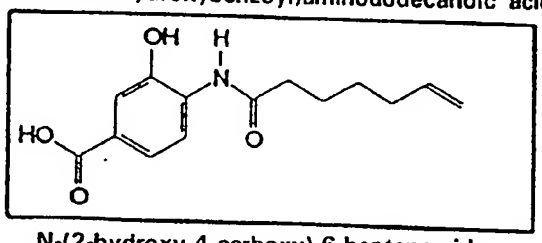
160

N-[3,5-dichloro-2-hydroxybenzoyl-3-(4-aminophenyl)]propionic acid



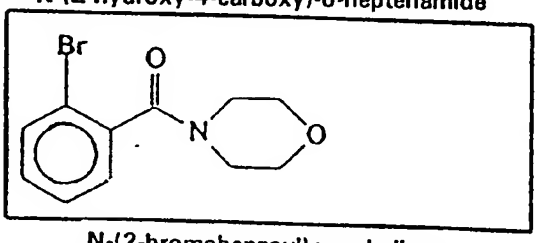
161

12-N-(3,5-dichloro-2-hydroxybenzoyl)aminododecanoic acid



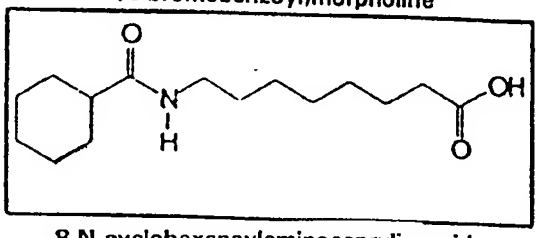
162

N-(2-hydroxy-4-carboxy)-6-heptenamide



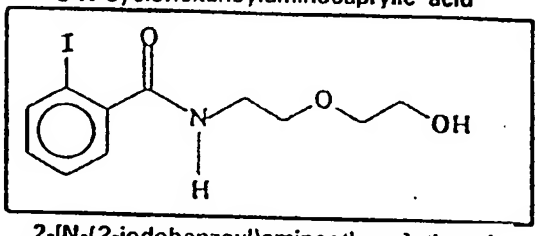
163

N-(2-bromobenzoyl)morpholine



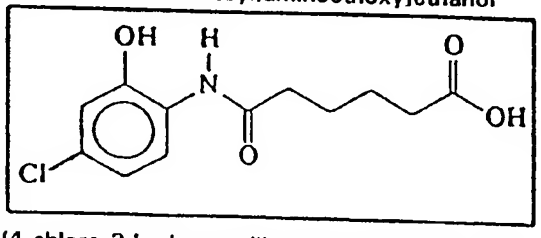
164

8-N-cyclohexanoylaminocaprylic acid



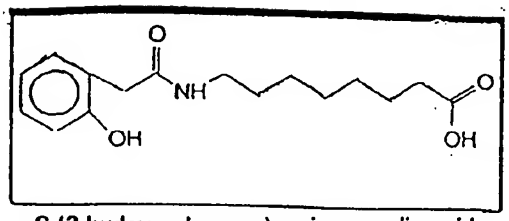
165

2-[N-(2-iodobenzoyl)aminoethoxy]ethanol



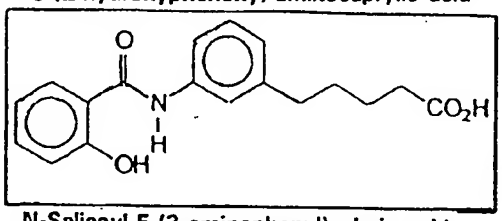
166

5-(4-chloro-2-hydroxyanilinocarbonyl)valeric acid



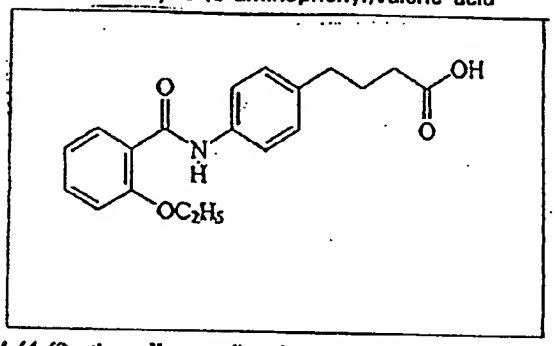
8-(2-hydroxyphenoxy)-aminocaprylic acid

167



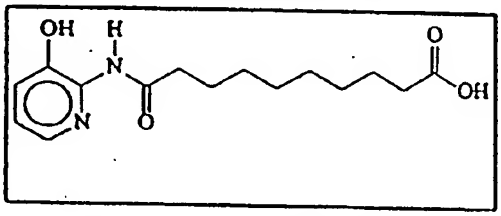
N-Salicoyl-5-(3-aminophenyl)valeric acid

168



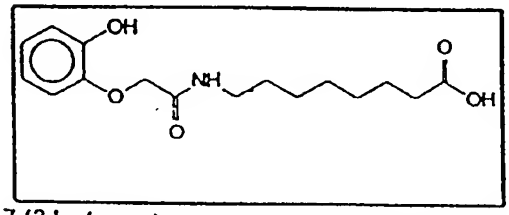
4-(4-(2-ethoxylbenzoyl)aminophenyl)butyric acid

169



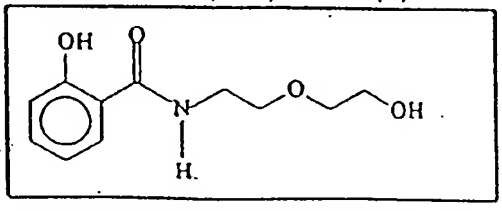
9-[2-(3-hydroxy)pyridylaminocarbonyl] nonanic acid

170



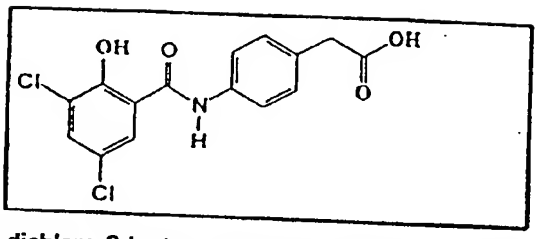
7-(2-hydroxyphenoxyacetyl)aminocaprylic acid

171



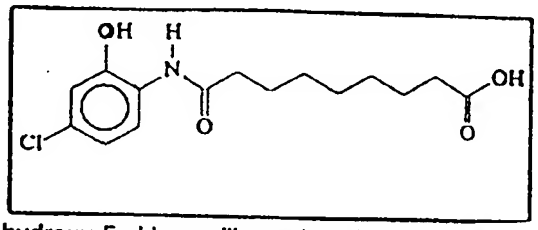
2-[N-(2-hydroxybenzoylamino)ethoxy]ethanol

172



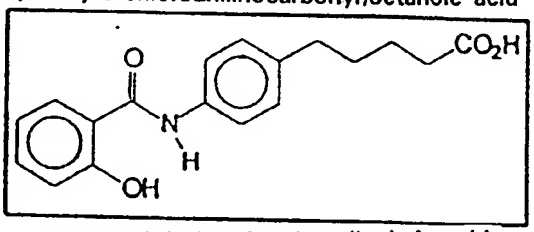
173

4-[N-(3,5-dichloro-2-hydroxybenzoyl)]aminophenylacetic acid



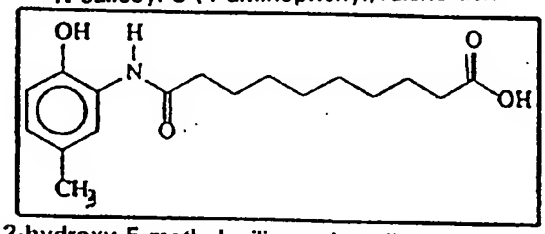
174

8-(2-hydroxy-5-chloroanilinocarbonyl)octanoic acid



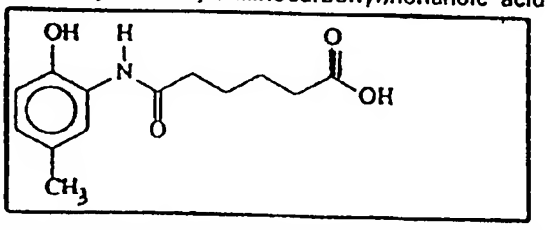
175

N-salicoyl-5-(4-aminophenyl)valeric acid



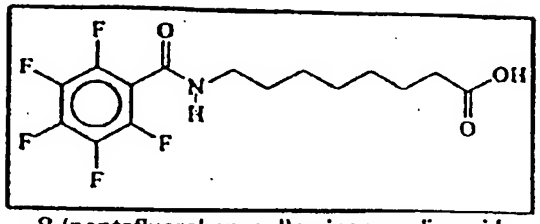
176

9-(2-hydroxy-5-methylanilinocarbonyl)nonanoic acid



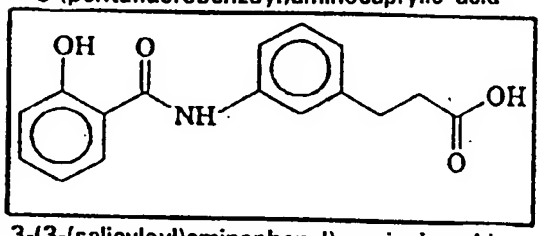
177

5-(2-hydroxy-5-methylanilinocarbonyl)valeric acid



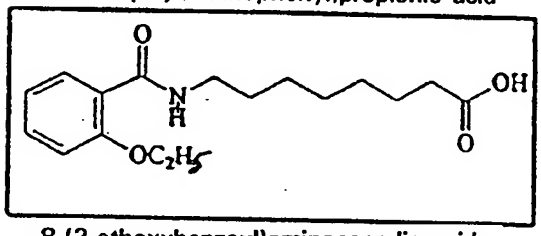
178

8-(pentafluorobenzoyl)aminocaprylic acid



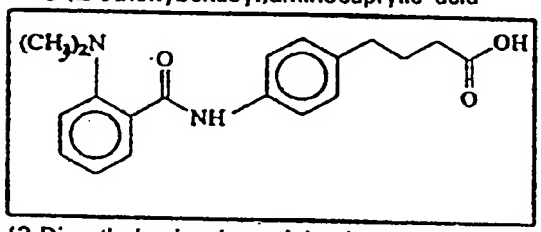
179

3-(3-(salicyloyl)aminophenyl)propionic acid



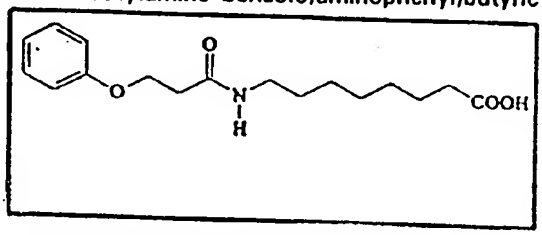
180

8-(2-ethoxybenzoyl)aminocaprylic acid



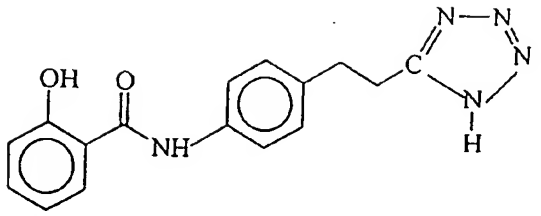
181

4-(4-(2-Dimethylamino benzoic)aminophenyl)butyric acid



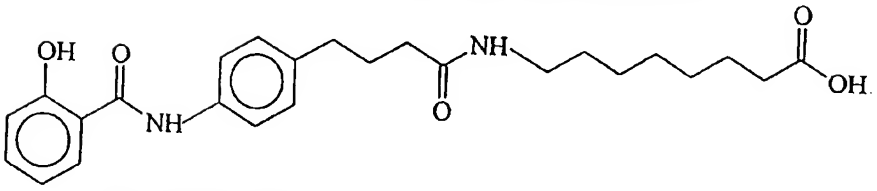
182

8-(3-Phenoxylpropionylamino)caprylic acid



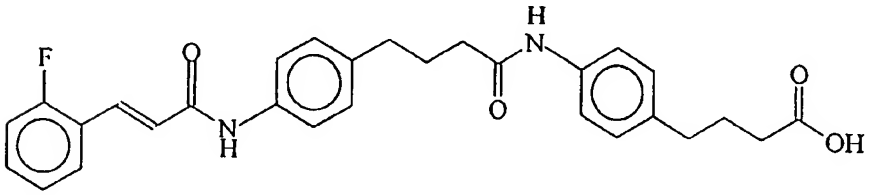
183

4-(Salicyloyl)aminophenylethyltetrazole



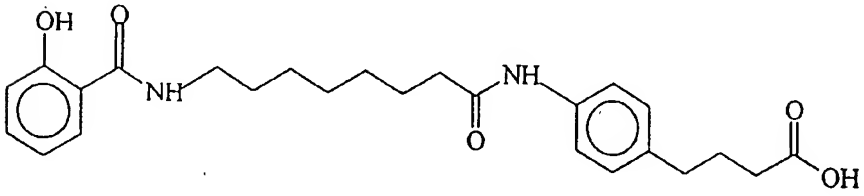
184

8(-(4(N-Saliciloyl-4aminophenyl)butyric)aminocaprylic acid [sic]



185

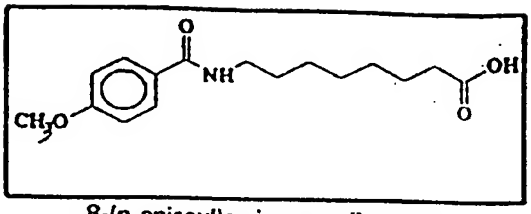
4-(4-(N-(2-Fluorocinnamoyl))aminophenyl) butyric



186

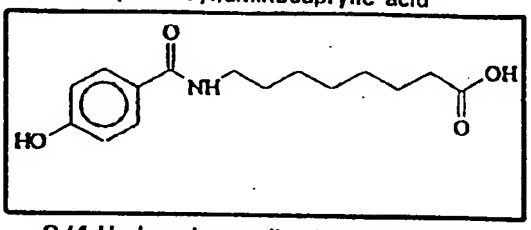
4-(4-(N-8(N-Salicyloyl)aminocaprylic)aminophenyl)butyric acid

187



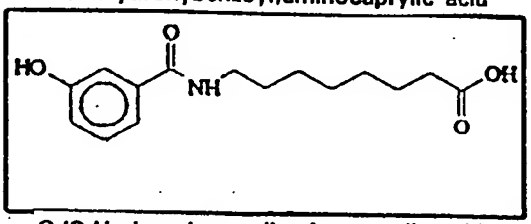
8-(p-anisoyl)aminocaprylic acid

188



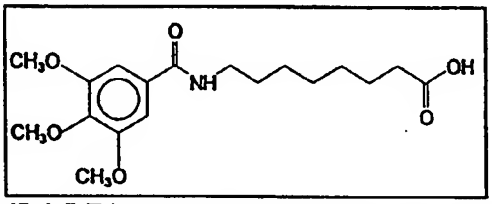
8-(4-Hydroxybenzoyl)aminocaprylic acid

189



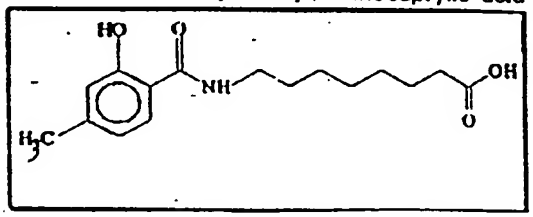
8-(3-Hydroxybenzoyl)aminocaprylic acid

190



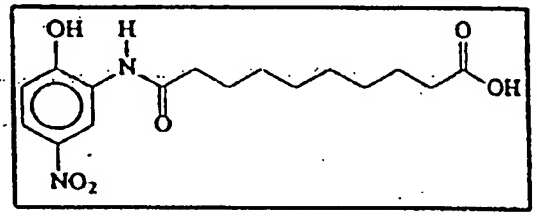
8-(3,4,5-Trimethoxybenzoyl)aminocaprylic acid

191



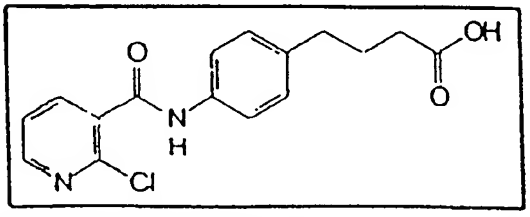
8-(N-4-Methylsalicyloyl)aminocaprillic acid [sic]

192



N-10-(2-hydroxy-5-nitroanilino)decanoic acid

193



4-(4-(2-chloronicotinoyl)aminophenyl)butyric acid

Compositions comprising the carrier compounds discussed above and active agents are effective in delivering active agents to selected biological systems.

DETAILED DESCRIPTION OF THE INVENTION

The specific compositions of the present invention include an active agent and a carrier. These compositions may be used to deliver various active agents through various biological, chemical, and physical barriers and are particularly suited for delivering active agents which are subject to environmental degradation. The compositions of the subject invention are particularly useful for delivering or administering biologically or chemically active agents to any animals such as birds including, but not limited to, chickens; mammals, such as primates and particularly humans; and insects.

Other advantages of the present invention include the use of easy to prepare, inexpensive raw materials. The compositions and the formulation methods of the present invention are cost effective, simple to perform, and amenable to industrial scale up for commercial production.

Subcutaneous, sublingual, and intranasal coadministration of an active agent, such as, for example, recombinant human growth hormone (rhGH); salmon calcitonin; heparin, including, but not limited to, low molecular weight heparin; parathyroid hormone; and compounds in compositions as described herein result in an increased bioavailability of the active agent compared to administration of the active agent alone.

Active Agents

Active agents suitable for use in the present invention include biologically or chemically active agents, chemically active agents, including, but not limited to, fragrances, as well as other active agents such as, for example, cosmetics.

Biologically or chemically active agents include, but are not limited to, pesticides, pharmacological agents, and therapeutic agents. For example, biologically or chemically active agents suitable for use in the present invention include, but are not limited to, peptides, and particularly small peptides; hormones, and particularly hormones which by themselves do not or only a fraction of the administered dose passes through the gastro-intestinal mucosa and/or are susceptible to chemical cleavage by acids and enzymes in the gastro-intestinal tract; polysaccharides, and particularly mixtures of muco-polysaccharides; carbohydrates; lipids; or any combination thereof. Further examples include, but are not limited to, human growth hormones; bovine growth hormones; growth releasing hormones; interferons; interleukin-1; insulin; heparin, and particularly low molecular weight heparin; calcitonin; erythropoietin; atrial naturetic factor; antigens; monoclonal antibodies; somatostatin; adrenocorticotropin, gonadotropin releasing hormone; oxytocin; vasopressin; cromolyn sodium (sodium or disodium chromoglycate); vancomycin; desferrioxamine (DFO); parathyroid hormone anti-microbials, including, but not limited to anti-fungal agents; or any combination thereof.

Carriers

Although compounds 1-193 above have been found to act as carriers for the oral delivery of biologically or chemically active agents, special mention is made of compounds 9, 35, 64, 67, 79, 102, 109, 111, 117, 122, 136, and 141, above.

Properties of compounds 1-193 are listed in Table 1, below.

TABLE 1 - Carrier Properties									
Compound	Anal. Calculated For				Found				Melting Point (°C)
	C	H	N	S	C	H	N	S	
1	48.8	4.70	4.40		48.81	4.64	4.39		
2	64.73	7.97	10.06		64.54	7.81	10.19		
3	55.33	5.80	4.03		55.40	5.79	3.96		69-71
4	62.64	6.06	5.62		62.75	6.08	5.51		151-154
5	65.16	6.11	13.40		65.29	6.03	13.29		144-145
6	54.70	3.24	3.75		54.29	3.24	3.54		165-169
7	69.00	6.11	4.47		69.09	6.24	4.43		126-129
9	65.51	7.90	4.78		65.60	8.25	4.83		89-90
9	68.99	6.11	4.47		69.01	6.08	4.47		104-107
10	52.74	4.42	7.69		52.91	4.45	7.49		142-145
11	48.83	5.85	8.14		48.95	5.89	8.02		120-122
12	69.71	6.47	4.28		69.56	6.47	4.38		144-146
13	65.51	7.90	4.77		65.23	7.88	4.72		72.5-74.5
14	60.17	5.36	4.39	10.04	60.09	5.36	4.35	9.99	155-156
15	52.38	4.79	11.11		52.45	4.94	11.08		220-222
16	67.60	5.95	3.94		67.34	6.01	3.91		219-222
17	68.09	6.53	3.78		67.77	6.24	3.81		130-133
18	54.13	5.30	10.52		54.12	5.24	10.54		192.5-195.5
19	55.26	4.21	7.16		54.48	4.32	6.86		>280 dec
20	65.51	7.90	4.77		65.52	7.90	4.77		75-80
21	58.85	7.21	15.84		58.86	7.16	15.69		120-122
22	63.15	5.30	14.73		63.30	5.43	14.18		197-201
23	64.04	5.66	7.86		64.17	5.67	7.75		188-190
24	69.91	6.88	8.46		69.98	6.79	8.58		131-134
25	58.36	4.56	12.76		58.20	4.63	12.61		138-141
26	56.98	3.94	7.82		56.39	3.92	7.74		221-223

TABLE 1 - Carrier Properties

Compound	Anal. Calculated For				Found				Melting Point (°C)
	C	H	N	S	C	H	N	S	
27	55.33	5.80	4.03		55.47	6.10	4.04		70-72
28									
29	65.74	7.58	4.79		65.51	7.89	4.78		52-55
30	64.50	7.57	5.02		64.07	7.81	5.40		70-74
31	54.70	5.17	3.99		54.50	4.99	3.95		173-174
32	58.63	5.94	9.12		58.73	6.20	10.34		125-129
33	69.00	6.10	4.47		69.18	6.08	4.54		100-102
34	63.99	5.37	9.33		63.46	5.35	9.06		218-221c
35	65.5	7.90	4.78		65.37	8.00	4.66		96-97C
36	68.22	5.72	4.68		67.88	5.65	4.55		134-137
37	63.14	7.23	6.69		63.15	7.29	6.58		53.5-56
38	60.00	7.14	10.00		59.78	7.31	9.94		135-138
39	61.67	4.41	10.29		61.69	4.41	10.12		>225
40	55.39	4.65	7.18		55.52	4.77	7.30		162.5-166
41	56.10	6.52	20.14		55.66	6.71	19.69		129-131
42	65.24	6.39	4.23		65.42	6.16	3.78		130-133.5
43	70.59	7.96	4.84		70.35	8.13	4.79		111-113
44	68.37	4.88	3.99		68.61	4.89	3.79		120-123
45	70.59	7.96	4.84		70.48	7.97	4.71		108-110
46	60.75	6.37	5.90		60.97	6.18	5.80		100.5-103
47	64.50	7.57	5.02		64.42	7.58	5.01		97-100
48	64.86	5.98	7.56		64.50	6.01	7.52		165-169
49	72.18	3.76	0.00		72.13	3.84	0.00		>225
50	72.51	8.76	4.23		72.39	8.84	4.12		120-122
51	64.50	7.58	5.01		64.75	7.65	4.69		200.5-204

TABLE 1 - Carrier Properties

Compound	Anal. Calculated For				Found				Melting Point (°C)
	C	H	N	S	C	H	N	S	
52		7.74	4.33			7.82	4.30		88-89
53	65.24	6.39	4.23		65.15	6.46	4.23		93-97
54	60.49	6.77	4.70		60.54	6.76	4.65		114-116
55	64.04	7.17	4.98		63.90	7.11	4.93		105-106
56	61.00	7.17	4.74		60.49	6.92	4.65		146-148
57	63.14	7.79	4.33		63.22	7.82	4.36		59-61
58	63.14	7.79	4.33		63.17	7.86	4.26		102-104
59	63.14	7.79	4.33		63.35	7.68	4.20		89-90
60	60.15	6.64	3.69		59.84	6.66	3.64		112-113
61	65.53	8.85	6.65		65.34	8.73	6.67		89-92
62	61.00	7.17	4.74		60.94	7.12	4.49		104-108
63	66.43	8.20	4.56		66.29	8.23	4.36		77-78
64	65.51	7.90	4.77		65.52	8.06	4.54		97-98
65	69.59	9.28	4.77		69.64	9.35	4.86		62-65
66	68.41	8.04	5.32		68.41	8.06	5.28		88-89
67	62.12	7.49	4.53		61.94	7.45	4.43		98-99
68	64.04	7.17	4.98		64.07	7.16	4.95		106-107
69	52.64	5.89	4.09		52.63	5.85	4.03		109-110
70	63.15	7.74	4.33		63.26	7.90	4.14		97-100
71	52.64	5.89	4.09		52.67	5.99	3.97		114-115
72	46.31	5.18	3.61		46.25	4.86	3.52		143-144
73	49.89	3.94	3.42		49.92	3.85	3.39		170-171
74	72.19	5.48	4.01		71.51	5.33	3.75		180
75	66.46	6.16	4.08		66.47	6.26	4.06		168.5-171
76	67.37	5.26	4.91		67.31	5.25	5.07		130-133
77	65.65	5.78	4.26		65.49	6.04	4.26		179-183
78	49.89	3.94	3.42		49.8	3.71	3.29		237-238

TABLE 1 - Carrier Properties

Compound	Anal. Calculated For				Found				Melting Point (°C)
	C	H	N	S	C	H	N	S	
79	65.65	5.78	4.26		65.21	6.05	4.24		156-158
80	56.38	4.45	3.87		56.4	4.21	3.91		130-131
81	56.38	4.45	3.87		56.46	4.5	3.84		197-198
82	56.6	7.49	4.4		56.3	7.49	4.14		58-62
83	57.03	8.2	3.91		57.17	7.8	3.7		138-140
84	57.58	7.11	3.95		57.52	7.7	3.94		
85	56.38	4.45	3.87		56.31	4.25	3.64		230-231
86	57.42	6.42	4.46		57.14	6.45	4.2		116-117
87	61	7.17	4.74		61.18	7.05	4.65		108-109
88	62.12	7.49	4.53		62.34	7.21	4.39		107-109
89	58.63	6.76	4.27		58.53	6.81	4.2		117-118
90	66.46	6.16	4.08		66.18	6.15	3.84		100-104
91	62.16	5.21	4.03		61.93	4.97	3.86		183-185
92	62.16	5.21	4.03		62.2	5.14	3.98		167-170
93	58.63	6.76	4.27		58.64	6.83	4.19		106-108
94	65.65	5.81	4.25		65.56	5.64	4.2		153-156
95	49.89	3.94	3.42		49.9	3.81	3.18		216-217
96	69.82	7.64	5.09		69.91	7.66	5.02		129-131
97	46.31	5.18	3.61		46.54	4.95	3.64		122-123
98	56.8	6.55	8.28		56.69	6.67	8.1		
99	56.8	6.55	8.28		57.37	6.57	8.33		117-118
100	60.33	5.06	7.82		59.98	4.97	7.67		207-209
101	66.46	6.16	4.08		66.37	6.32	3.96		126-128
102	50.29	5.63	3.91		50.14	5.7	3.76		129-131
103	70.93	5.95	6.89		70.94	6.44	6.89		
104	65.84	6.14	8.53		65.94	6.19	8.54		228-231
105	64.96	5.77	8.91		64.89	5.82	8.82		

TABLE 1 - Carrier Properties

Compound	Anal. Calculated For				Found				Melting Point (°C)
	C	H	N	S	C	H	N	S	
106	66.65	6.48	8.18		66.39	6.49	8.05		140-142
107	66.47	6.12	4.07		66.5	6.26	4.08		140-142
108	60.33	5.06	7.82		60.32	4.99	7.78		150-151
109	57.41	6.42	4.46		57.07	6.44	4.39		121-123
110	44.46	4.97	3.46						133-135
111	69.28	7.03	4.25		68.86	7.07	4.11		147-149
112	55.55	6.22	8.64		55.27	5.99	8.5		120-121
113	53.99	4.26	3.7		53.98	4.25	3.63		210 decom
114	57.49	7.39	4.74		57.72	7.57	4.43		80-83
115	65.5	7.9	4.77		64.97	7.79	4.75		90-92
116	65.5	7.9	4.77		65.11	8.03	4.71		125-127
117	71.26	8.3	4.2		70.6	7.89	4.83		94-96
118	56.29	4.17	7.72		56.23	4.01	7.6		173-175
119	47.89	3.81	3.29		47.52	3.71	3.16		236-237
120	55.7	6.55	13		55.71	6.58	13.05		123-5
121	57.98	5.81	7.95		57.9	7.11	7.82		131-133
122	51.74	5.5	4.02		51.41	5.43	3.61		118-119.5
123	41.22	4.38	3.2		41.45	4.36	2.94		143-144.5
124	57.06	6.06	4.44		57.02	6.12	4.35		57-58
125	61.18	4.83	4.2		60.71	4.76	3.89		214 decom
126	55.55	6.22	8.64		55.4	6.24	8.53		150-151
127	65.17	4.83	4.47		65.27	4.87	4.48		208-209
128	73.03	8.99	4.06		72.92	9.36	4.1		99-101
129	72.25	5.44	4		72.14	5.24	4.01		216-217
130	52.56	5.58	8.17		52.66	5.44	8.21		96-100

TABLE 1 - Carrier Properties

Compound	Anal. Calculated For				Found				Melting Point (°C)
	C	H	N	S	C	H	N	S	
131	56.28	6.41	9.38		56.32	6.42	9.28		98-100
132	52.56	5.58	8.17		52.46	5.65	7.86		150-153
133	69.89	4.89	4.53		69.64	5	4.54		136-9
134	71.68	5.2	4.2		71.24	5.1	4.13		251-253
135	65.64	5.78	4.25		65.3	5.91	4.04		79-83
136	33.92	3.61	2.64		34.48	3.84	2.48		164-165
137	57.06	6.06	4.44		57.09	6.17	4.45		88-89
138	69.79	7.69	5.09		69.68	7.78	5.08		102-3
139	69.28	7.04	4.25		68.99	7	4.1		107-108
140	66.42	6.62	4.84		66.2	6.49	4.81		88-9
141	58.62	6.76	4.27		58.66	6.93	4.18		134-135
142	63.38	7.21	5.28		63.22	7.28	5.24		71-73
143	56.29	4.17	7.72		56.19	4.04	7.65		156-160
144	71.13	7.88	3.77		70.39	7.91	3.64		95-97
145	58.44	6.06	8.02		58.25	6.38	7.84		165-8
146	54.22	5.79	5.75		54.26	5.65	5.69		77-78.5
147	54.22	5.79	5.75		54.21	5.85	5.61		80-81
148	58.78	4.93	40.3		58.64	4.89	3.97		172-173
149	56.19	4.72	3.85		56.31	4.67	3.86		177
150	66.46	4.65	4.31		66.41	4.56	4.23		158-160
151	58.61	7.24	5.69		58.79	7.35	5.66		
152	54.22	5.79	5.75		54.21	5.72	5.62		54-55
153	60.85	4.25	7.89		60.27	4.37	7.89		>260
154	62.5	7.3	10.14		64.77	7.27	9.9		187-190
155	55.4	6.5	3.6		55.56	6.51	3.5		114-116
155	45.85	4.9	4.86		46.06	4.78	4.71		67-68
156	48.8	4.7	4.4		48.81	4.64	4.39		144-146

TABLE 1 - Carrier Properties

Compound	Anal. Calculated For				Found				Melting Point (°C)
	C	H	N	S	C	H	N	S	
157	50.3	5.1	4.2		50.25	5.12	3.99		141-143
158	55.5	4.1	3.8		55.55	3.88	3.75		190-192
159	64.97	6.9	5.05		64.7	6.82	5.02		171-174
160	54.3	3.7	4		54.31	3.58	3.83		222-224
161	56.4	6.7	3.5		56.69	6.98	3.11		76-78
162	63.63	6.47	5.3		64.76	6.84	4.74		188-191
163	48.91	4.48	5.19		48.89	4.31	5.10		88.5-90
164	66.66	10.04	5.18		66.69	10.77	5.16		67.5-70.5
165	39.42	4.21	4.18		39.19	4.35	3.88		oil
166	53.05	5.19	5.16		53.06	5.03	4.86		151-152
167	65.53	7.85	4.78		65.4	7.84	4.57		85-89
168	68.99	6.11	4.47		68.62	5.87	4.49		162-6
169	69.71	6.47	4.28		69.67	6.58	4.50		132.5-135
170	61.21	7.53	9.52		61.21	7.68	9.46		134-135
171	62.14	7.44	4.53		61.96	7.52	4.57		101-104
172	58.63	6.71	6.22		58.15	6.83	6.04		
173	52.96	3.26	4.12		52.96	3.28	4.02		225-227
174	57.42	6.42	4.46		57.3	6.38	4.39		119-120
175	68.99	6.11	4.47		68.84	6.08	4.51		131-4
176	66.43	8.2	4.56		66.42	8.16	4.51		109-110
177	62.14	6.82	5.57		61.96	6.66	5.52		127-128
178	51.00	4.56	3.97		51.09	4.61	3.93		
179	67.36	5.30	4.90		67.26	5.24	4.91		185-186
180	66.43	8.20	4.56		66.32	8.60	5.12		51.5-55
181	69.92	6.79	8.58		67.02	6.93	8.20		81-84
182	66.46	8.14	4.56		66.43	8.34	4.47		82-84
183	62.13	4.89	22.64		62.05	4.88	22.45		271-272

TABLE 1 - Carrier Properties

Compound	Anal. Calculated For				Found				Melting Point (°C)
	C	H	N	S	C	H	N	S	
184	68.16	7.32	6.36		67.73	7.44	6.70		114-117
185	71.30	5.98	5.73		71.10	5.97	5.74		146-149
186	68.16	7.32	6.36		67.94	7.31	6.41		105-108
187	65.51	7.90	4.77		65.35	7.63	4.59		102-103
188	64.50	7.58	5.01		64.19	7.69	4.83		133-134
189	64.5	7.58	5.01		64.5	7.57	4.90		116-118
190	61.15	7.71	3.97		61.27	7.79	4.08		124-127
191	65.5	7.9	4.77		65.32	7.94	4.7		114-115
192	56.77	6.51	8.28		56.83	6.76	8.21		141-143
193	60.29	4.74	8.79		60.17	4.58	8.74		202-205
194	48.8	4.7	4.4		48.81	4 .64	4.39		144-146

These carrier compounds or poly amino acids, and peptides, including the amino acids, may be used to deliver active agents including, but not limited to, biologically or chemically active agents such as for example, pharmacological and therapeutic agents.

An amino acid is any carboxylic acid having at least one free amine group and includes naturally occurring and synthetic amino acids.

Poly amino acids are either peptides or two or more amino acids linked by a bond formed by other groups which can be linked, e.g. an ester, anhydride, or an anhydride linkage.

Peptides are two or more amino acids joined by a peptide bond. Peptides can vary in length from dipeptides with two amino acids to poly peptides with several hundred amino acids. See Chambers Biological Dictionary, editor Peter M. B. Walker, Cambridge, England: Chambers Cambridge, 1989, page 215. Special mention is made of di-peptides, tri-peptides, tetra-peptides, and penta-peptides.

Salts such as, for example, sodium salt of these carrier compounds can be used as well.

Many of the compounds described herein are derived from amino acids.

Many of the compounds of the present invention can be readily prepared from amino acids including, but not limited to, aminocaprylic acid, butyrylhydroxaminic acid, aminophenylbutyric acid, aminophenylhexanoic acid, aminophenylpropionic acid, amino salicylic acid, aminophenylsuccinic acid, aminononanic acid, aminonicotinic acid, amino valenic acid, aminophenylacetic acid, aminocaproic acid, aminoundecanoic acid, aminoheptanoic acid, aminohydroxybenzoic acid, and aminodecanoic acid by methods within the skill of those in the art based upon the present disclosure and the methods described in U.S. patent application serial nos. 60/017,902, filed March 29, 1996; 08/414,654, filed March 31, 1995; 08/335,148, filed October 25, 1994; and 60/003,111, filed September 1, 1995.

For example, these compounds may be prepared by reacting the single acid with the appropriate agent which reacts with free amino moiety present in the amino acids to form amides. Protecting groups may be used to avoid unwanted side reactions as would be known to those skilled in the art.

The carrier compound may be purified by recrystallization or by fractionation on solid column supports. Suitable recrystallization solvent systems include acetonitrile, methanol and tetrahydrofuran. Fractionation may be performed on a suitable solid column supports such as alumina, using methanol/n-propanol mixtures as the mobile phase; reverse phase column supports using trifluoroacetic acid/acetonitrile mixtures as the mobile phase; and ion exchange chromatography using water as the mobile phase. When anion exchange chromatography is performed, preferably a subsequent 0-500 mM sodium chloride gradient is employed.

Delivery Systems

The compositions of the present invention may include one or more active agents.

In one embodiment, compounds or salts of compounds 1-193 or poly amino acids or peptides that include at least one of these compounds or salts may be used directly as a delivery carrier by simply mixing one or more compound or salt, poly amino acid or peptide with the active agent prior to administration.

The administration mixtures are prepared by mixing an aqueous solution of the carrier with an aqueous solution of the active ingredient, just prior to administration. Alternatively, the carrier and the biologically or chemically active ingredient can be admixed during the manufacturing process. The solutions may optionally contain additives such as phosphate buffer salts, citric acid, acetic acid, gelatin, and gum acacia.

Stabilizing additives may be incorporated into the carrier solution. With some drugs, the presence of such additives promotes the stability and dispersibility of the agent in solution.

The stabilizing additives may be employed at a concentration ranging between about 0.1 and 5 % (W/V), preferably about 0.5 % (W/V). Suitable, but non-limiting, examples of stabilizing additives include gum acacia, gelatin, methyl cellulose, polyethylene glycol, carboxylic acids and salts thereof, and polylysine. The preferred stabilizing additives are gum acacia, gelatin and methyl cellulose.

The amount of active agent is an amount effective to accomplish the purpose of the particular active agent. The amount in the composition typically is a pharmacologically, biologically, therapeutically, or chemically effective amount. However, the amount can be less than a pharmacologically, biologically, therapeutically, or chemically effective amount when the composition is used in a dosage unit form, such as a capsule, a tablet or a liquid, because the dosage unit form may contain a multiplicity of carrier/biologically or chemically active agent compositions or may contain a divided pharmacologically, biologically,

therapeutically, or chemically effective amount. The total effective amounts can then be administered in cumulative units containing, in total, pharmacologically, biologically, therapeutically or chemically active amounts of biologically or pharmacologically active agent.

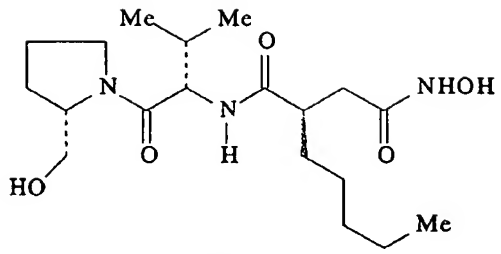
The total amount of active agent, and particularly biologically or chemically active agent, to be used can be determined by those skilled in the art. However, it has surprisingly been found that with some biologically or chemically active agents, the use of the presently disclosed carriers provides extremely efficient delivery, particularly in oral, intranasal, sublingual, intraduodenal, rectal, vaginal, buccal, ophthalmic, or subcutaneous systems as well as systems for crossing the blood/brain barrier. Therefore, lower amounts of biologically or chemically active agent than those used in prior dosage unit forms or delivery systems can be administered to the subject, while still achieving the same blood levels and therapeutic effects.

The amount of carrier in the present composition is a delivery effective amount and can be determined for any particular carrier or biologically or chemically active agent by methods known to those skilled in the art.

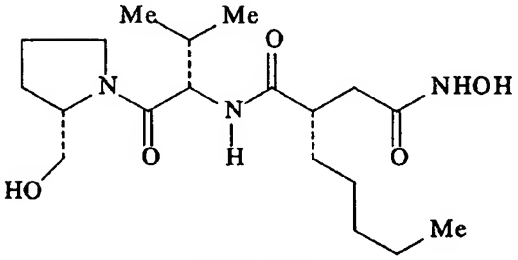
Dosage unit forms can also include any of excipients; diluents; disintegrants; lubricants; plasticizers; colorants; and dosing vehicles, including, but not limited to water, 1,2-propane diol, ethanol, olive oil, or any combination thereof.

Administration of the present compositions or dosage unit forms preferably is oral or by intraduodenal injection.

The delivery compositions of the present invention may also include one or more enzyme inhibitors. Such enzyme inhibitors include, but are not limited to, compounds such as actinonin or epiactinonin and derivatives thereof. These compounds have the formulas below:

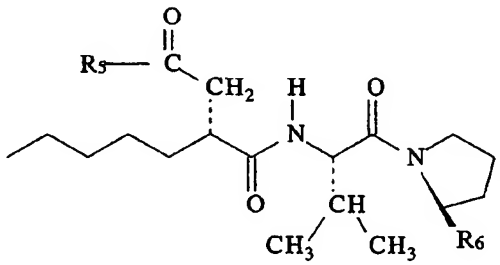


Actinonin



Epiactinonin

Derivatives of these compounds are disclosed in U.S. Patent No. 5,206,384. Actinonin derivatives have the formula:



wherein R^5 is sulfoxymethyl or carboxyl or a substituted carboxy group selected from carboxamide, hydroxyaminocarbonyl and alkoxycarbonyl groups; and R^6 is hydroxyl, alkoxy, hydroxyamino or sulfoxyamino group. Other enzyme inhibitors include, but are not limited to, aprotinin (Trasylol) and Bowman-Birk inhibitor.

The compounds and compositions of the subject invention are useful for administering biologically or chemically active agents to any animals such as birds; mammals, such as primates and particularly humans; and insects. The system is particularly advantageous for delivering chemically or biologically or chemically active agents which would otherwise be destroyed or rendered less effective by conditions encountered before the active agent its target zone (i.e. the area in which the active agent of the delivery composition are to be released) and within the body of the animal to which they are administered. Particularly, the compounds and compositions of the present invention are useful in orally administering active agents, especially those which are not ordinarily orally deliverable.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate the invention without limitation. All parts are given by weight unless otherwise indicated.

Example 1 - Carrier Preparation

General Preparations of Carriers. The following procedures were used to prepare the compounds described herein. Many of the compounds were prepared by reaction of the appropriate amino acid with the appropriate acid chloride. The preparation of compound 79 is given as a representative example of the compounds prepared in this manner.

Preparation of Compound 79. Method A. A 1 L round bottom flask fitted with a magnetic stirrer was charged with 3-(4-aminophenyl)propionic acid (46.3 g, 0.28 moles, 1.17 equiv.) and 2 M aqueous sodium hydroxide (300 mL).

2,3-dimethoxybenzoylchloride (48.0 g, 0.24 moles, 1.00 equiv.) was added portionwise over 1 h to the stirred solution. After the addition, the reaction was stirred for 2.5 h at ambient temperature, and the pH of the solution was kept at *ca* 10 by the addition of 10 M sodium hydroxide. The solution was then acidified with 1 M hydrochloric acid (3 x 100 mL), water (100 mL), and air dried. It was redissolved in boiling acetone (*ca* 500 mL), decolorized with activated charcoal (3g), and filtered. Water (1.5 L) was added to the filtrate to induce the formation of a brown oil. The brown oil solidified upon stirring at room temperature for 10 min. The crude solid was collected by filtration and recrystallized from 70% methanol-water (v/v) to afford compound 79 as a tan solid (39.5) g, 50%).

Compounds 1, 5, 30, 31, 33, 36, 53-66, 68, 69, 71-74, 78, 80-88, 95, 97-99, 102, 108-110, 112-115, 119, 121-126, 136, 137, 139, 141, 144, 146, 147, 151, 152, 155-158, 160, 161, 163, 165, 166, 170, 172-174, 176, 177, 184-186, 188, 189, 191 and 192 were also prepared by this process.

Preparation of Compound 79. Method B. A 2 L three-neck round bottom flask was fitted with a magnetic stirrer and two addition funnels under an argon atmosphere. A suspension of 3-(4-aminophenyl)propionic acid (46.3 g, 0.28 moles, 1.17 equiv.) in ethyl acetate (700 mL) was added to the flask. A solution of 2,3-dimethoxybenzoylchloride (48.0 g, 0.24 moles, 1.00 equiv.) in ethyl acetate (250 mL) was charged to one of the addition funnels and added dropwise over 1 h. Triethylamine (28.20 g, 0.28 moles, 1.00 equiv.) was subsequently charged to the second funnel and added dropwise over 15 min. The reaction was stirred at ambient temperature for 3 h, and the solvent was evaporated *in vacuo* giving a residual brown oil. Water (600 mL) was added to the residue followed by sodium hydroxide (2 M, 500 mL), and the mixture was stirred at ambient temperature for 3 hours. The resultant brown solution was acidified with 2 M hydrochloric acid (*ca* 1 L). After cooling the mixture in an ice bath for 1 h, a yellow solid formed and was collected by filtration. The solid was washed with water (3 x 1.5 L) and

recrystallized from 50% ethanol-water (v/v) to give compound 79 as a tan solid (59.2 g, 68%).

Compounds 18, 32, 37, 41, 168, 175, and 183 were also prepared by this process.

Preparation of Compound 79. Method C. A 2 L round bottom flask equipped with a magnetic stirrer and a reflux condenser was charged with a suspension of 3-(4-aminophenyl)propionic acid (46.3 g, 0.28 moles, 1.17 equiv.) in dichloromethane (560 mL). Chlorotrimethylsilane (62.36 g, 0.57 moles, 2.05 equiv.) was added in one portion, and the mixture was heated to reflux for 1 h under argon. The reaction was allowed to cool to room temperature and was placed in an ice bath (internal temperature $<10°C$). The reflux condenser was replaced with an addition funnel containing triethylamine (42.50 g, 0.42 moles, 1.50 equiv.). The triethylamine was added dropwise over 15 min, and a yellow solid formed during the addition. The funnel was replaced by another addition funnel containing a solution of 2,3-dimethoxybenzoylchloride (48.0 g, 0.24 moles, 1.00 equiv. in dichloromethane (100 mL). The solution was added dropwise over 30 min. The reaction was stirred in the ice bath for another 30 min and at ambient temperature for 1 h. The dichloromethane was evaporated *in vacuo* to give a brown oil. The brown oil was cooled in an ice bath, and an ice-cold solution of 2 M sodium hydroxide (700 mL) was added. The ice bath was removed, and the reaction was stirred for 2 h to afford a clear brown solution. The solution was acidified with 2 M sulfuric acid (400 mL) and stored at *ca* 5°C for 1 hour. A yellow solid formed and was collected by filtration. The solid was washed with water (3 x 100 mL) and recrystallized from 50% ethanol-water (v/v) to afford compound 79 as tan needles (64.7 g, 82%).

Compounds 2-4, 6-17, 19-29, 34, 38-40, 42-48, 50-52, 67, 70, 75-77, 89-94, 96, 100, 101, 107, 111, 116-118, 127-132, 134, 135, 193, 142, 143, 148, 149, 159, 162, 164, 169, 178-182, 187, and 190 were also prepared by this process.

Preparation of Compound 35. A solution of *O*-acetylsalicyloyl chloride (24.68 g, 124 mmol, 1 equiv) in tetrahydrofuran (300 mL) was cooled in an ice bath. Triethylamine (25 g, 249 mmol, 2 equiv) was added dropwise via an additional funnel. The methyl 9-aminononanoate hydrochloride was dissolved in DMF (190 mL, slightly warm to dissolve), charged to an addition funnel and added dropwise to the above mixture. The reaction was stirred in the ice-bath for 20 min and at room temperature for 2 h. Evaporation of the THF under reduced pressure gave a pink DMF solution. The pink solution was cooled in an ice-bath, and 2 M aqueous sodium hydroxide (300 mL) was added. After being stirred at room temperature for 12 h, the mixture was acidified with 2 M hydrochloric acid (500 mL). The solution was cooled in an ice-bath, and a solid formed. The solid was collected by filtration and was recrystallized from 50% ethanol/water to give compound 35 (32 g, 87%) as an off-white solid.

Preparation of Compound 49. 1-(2-hydroxyphenyl)-3-(4-methyl benzoate)-1,3-propane dione (3.00 g, 0.0101 mil.) is placed in a 100 ml round bottomed flask fitted with argon purge, magnetic stir bar and cold water condenser. Glacial acetic acid (20 mls) and concentrated sulfuric acid (5 mls) were added, and heating of the reaction mixture was initiated. The reaction mixture was allowed to heat at reflux for 6 h before heating was discontinued. The reaction mixture was allowed to come to room temperature, and then was poured into 100 mls of ice/water. This was stirred for approximately 1/2 h before the mixture was filtered, and a brown solid was isolated. The brown solid was recrystallized twice from acetic acid, yielding compound 49 as a tan solid (1.44 g, 53.8%).

Preparation of Compound 167. 2-coumaranone (4.21 g, 0.0314 mol) was dissolved, with stirring, in acetonitrile (75 mls) in a 250 ml round bottomed flask fitted with a magnetic stir bar, argon purge and cold water condenser. Triethylamine (3.18 g, 0.0314 mol) and 8-aminocaprylic acid (5.00 g, 0.0314 mol) were added, and a tan slurry was formed. Heating was started, and the reaction

mixture was allowed to reflux overnight. After heating overnight, thin layer chromatography of the reaction mixture (50% ethyl acetate / 50% hexane) indicated that the reaction had gone to completion. Heating was stopped, the reaction mixture was allowed to cool to room temperature, and was concentrated *in vacuo*. The resulting residue was taken up in methylene chloride, and was washed with two, 100 ml portions of 1N hydrochloric acid solution. The methylene chloride layer was dried with sodium sulfate and was concentrated *in vacuo*. The resulting tan solid was allowed to dry *in vacuo* overnight, yielding compound 167 as a tan solid (8.35 g, 70.4%).

Preparation of Compound 171. 1,4-benzodioxan-2-one (3.93 g, 0.0262 mol) was dissolved, with stirring, in acetonitrile (70 mls) in a 250 ml round bottomed flask fitted with a magnetic stir bar, argon purge and cold water condenser. Triethylamine (2.64 g, 0.0262 mol) and 8-aminocaprylic acid (500 g, 0.0262 mol) were added and a tan slurry was formed. Heating was started, and the reaction mixture was allowed to reflux for approximately 3 hours. At this time, thin layer chromatography of the reaction mixture (50% ethyl acetate /50% hexane) indicated that the reaction had gone to completion. Heating was discontinued, and the reaction mixture was allowed to cool to room temperature and was concentrated *in vacuo*. The resulting residue was taken up in methylene chloride and was washed with a 100 ml portion of 1N hydrochloric acid solution. At this time, a tan solid was noted to precipitate, and it was isolated by filtration. This tan solid was washed further with an additional 100 ml portion of 1 N hydrochloric acid solution, and then with 100 ml of water. The resulting tan solid was allowed to dry *in vacuo* overnight yielding Compound 171 as a tan solid (7.73 g, 95.6%).

Preparation of Compound 120. A solution of 3.00 g (18.3 mmol) of 2-nitrophenylisocyanate and 5 mL of tetrahydrofuran was dropwise over 10 min to an ice bath-cooled solution of 2.08 g (13.1 mmol) of 8-aminocaprylic acid, 1.40 mL of 10 N NaOH and 40 mL of water. The reaction mixture was stirred an additional

30 min, warmed to 25°C and treated with 3% HCl solution until the pH was 5. The yellow precipitate was filtered off and rinsed with 100 ml of water. The yellow solid was recrystallized in 2-propanol and water to give 3.7 g of compound 120 as pale yellow crystals.

Compounds 104-106 were also prepared by this procedure.

Preparation of Compound 133. A suspension of 2.40 g (16.3 mmol) and 2.80 g (15.6 mmol) of 4-(4aminophenyl)butyric acid in 20 mL of propylene glycol, 2.40 mL (1.74 g, 17.3 mmol) of triethylamine and 10 mg (0.08 mmol) of dimethylaminopyridine was heated to 140°C. The mixture became a clear solution after 5 min at 140°C. After stirring for 330 min, the reaction mixture was cooled to 25°C and diluted with 20 mL of water. The solid phthalimide which had formed was filtered off. The filtrate was acidified with 3% HCl solution. The resulting solid was filtered off and was recrystallized from 2-propanol and water to give 0.62 g of compound 133 as a tan solid.

Preparation of Compound 138. A solution of 1.73 g (12.9 mmol) of phthalic dialdehyde, 2.04 g 8-aminocaprylic acid and 20 mL of acetic acid was heated to reflux for 10 min. The reaction mixture was cooled to 40°C, diluted with water and extracted with CH_2Cl_2 (2 X 20 mL). The organic phase was washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was dissolved in ether and extracted with 2N NaOH. The layers were separated. The aqueous layer was made acidic with 3% HCl and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and evaporated. The yellow residue was crystallized from acetonitrile and water to give 1.25 g of compound 138 as a yellow solid.

Preparation of Compound 140. A mixture of 1.40 g (9.48 mmol) of phthalic anhydride and 1.51 g (9.48 mmol) of 8-aminocaprylic acid was heated to 150°C for 5 min. Upon cooling, 2.61 g of solid compound 140 was received.

Compound 150 was also prepared by this procedure.

Preparation of Compound 145. A suspension of 2.11 g (10.1 mmol) ethyl carbamoylanthranilic acid and 5 mL of CH_2Cl_2 was treated with 2.20 mL of oxalyl chloride. After stirring for 1 h the volatiles were stripped off. At that same time, a suspension of 1.60 g (10.1 mmol) of 8-aminocaprylic acid and 15 mL of CH_2Cl_2 was treated with 2.60 mL (2.23 g, 20.5 mmol) of TMSCl. This mixture was heated to reflux for 90 min, cooled in an ice bath and treated with 4.30 mL (3.12 g, 30.9 mmol) of triethylamine. Five min later, a slurry of the residue from the oxalyl chloride reaction in 20 mL of CH_2Cl_2 was added. The reaction mixture was warmed to 25°C and stirred overnight. Upon acidification of the mixture with 3% HCl, a white solid formed. The solid was filtered off and recrystallized from EtOH and water to give 1.88 g of compound 145.

Compound 153 was also prepared by this procedure.

Preparation of Compound 154. A suspension of 4.02 g(25.6 mmol) of trans-4-aminomethylcyclohexane-carboxylic acid, 4.18 g (25.6 mmol) of isatoic anhydride, 20 mL of CH_2Cl_2, 20 mL of dioxane, and 4 mL of water was heated to reflux for 12 h. The solution was cooled to 25°C and extracted with ether (4 x 20 mL). The organic layer was dried over Na_2SO_4 and concentrated. The resulting solid was recrystallized from EtOH and water to give 4.95 g of compound 154.

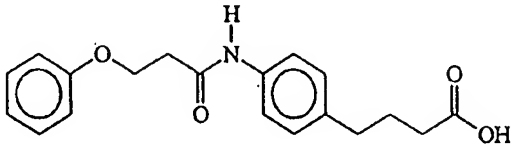
Compound 103 is available from Aldrich Chemical Company, Inc., Milwaukee, WI.

Example 2 - Parathyroid Hormone Dosing Solutions

Intracolonic ("IC") dosing compositions containing 100 mg/kg of carrier and 25 μg/kg of parathyroid hormone in 25% aqueous propylene glycol or oral gavage "PO") dosing solution containing 400 mg/kg of carrier and 100 μg/kg of parathyroid hormone in water, were prepared with carriers 9, 33, 35, 77, 79, 109, 110, 123, 136, 141, and 169. The dosing solutions are designated P- carrier number - DS.

Comparative Example 2A - Parathyroid Hormone Dosing Solutions

An intracolonic dosing composition containing 100 mg/kg of a carrier having the formula



and 25 ug/kg of parathyroid hormone in 25% aqueous propylene glycol was prepared. The dosing solution is identified as P-9A-DS.

Examples 3 - *In vivo* Parathyroid Hormone Delivery

Male Sprague-Dawley rats weighing between 200-250g were fasted for 24 hours and were administered ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing. The rats were administered one of dosing solutions P-9-DS, P-33-DS, P-35-DS, P-77-DS, P-79-DS, and P-141-DS by oral gavage ("PO") or intra-colonic instillation ("IC"). Blood samples were collected serially from the tail artery for serum determination of parathyroid hormone concentration. Serum parathyroid hormone concentrations were quantified by a parathyroid hormone immunoaccuracy test host.

Results are illustrated in Table 2, below.

Comparative Example 3A - *In vivo* Parathyroid Hormone Delivery

The procedure of Example 3 was followed substituting dosing solution P-9A-DS for dosing solution P-9-DS. Results are illustrated in Table 2, below.

Comparative Example 3B - *In vivo* Parathyroid Hormone Delivery

The procedure of Example 3 was followed with a dosing solution (at a dose of 25 μg/kg of parathyroid hormone (intra-colonic) or 100 μg/kg of parathyroid hormone (oral)), P-ØA-DS, that omitted the carrier.

Results are illustrated in Table 2, below.

TABLE 2 - *In vivo* Parathyroid Hormone Delivery

Dosing Solution	Mean Peak Serum [PTH] ± Standard Deviation (pg/ml)
P-9-DS	155 ± 105 (IC)
P-33-DS	58 ± 18 (IC)
P-35-DS	50 ± 27 (IC)
P-77-DS	358 ± 274 (PO)
P-79-DS	521 ± 128 (PO)
P-109-DS	128 ± 25 (IC)
P-110-DS	35 ± 11 (IC)
P-123-DS	49 ± 22 (IC)
P-136-DS	106 ± 72 (IC)
P-141-DS	120 ± 120 (PO)
P-169-DS	19 ± 33 (IC)
P-9A-DS	116 ± 48 (IC)
P-ØA-DS	11 ± 2 (PO), 27 ± 27 (IC)

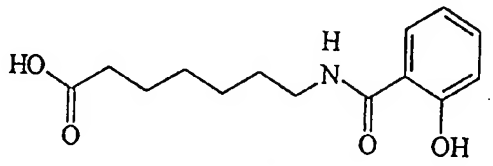
Examples 4 - Recombinant Human Growth Hormone Dosing Solutions

Intracolonic dosing compositions containing 25 mg/kg of carrier and 1 mg/kg of rHGH in phosphate buffer or oral gavage dosing solutions containing 600 mg/kg of carrier and 3 mg/kg of rHGH in phosphate buffer were prepared with carriers 9, 35, 36, 47, 62, 64, 67, 77, 79, 90, 94, 107, 109, 136, and 141.

The dosing solutions are designated R- carrier number - DS.

Comparative Example 4A - Recombinant Human Growth Hormone Dosing Solutions

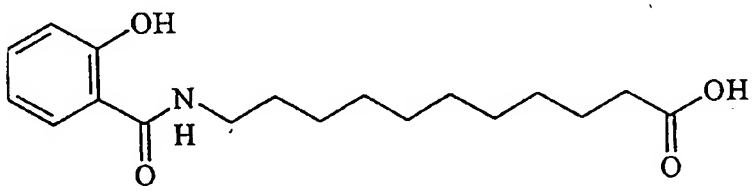
An intracolonic dosing solution was prepared according to the procedure of Example 4, substituting a carrier having the formula



for the carrier. This dosing solution is designated as R-35A-DS.

Comparative Example 4B - Recombinant Human Growth Hormone Dosing Solutions

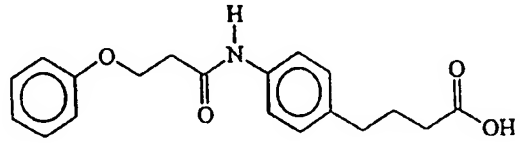
An intracolonic dosing solution was prepared according to the procedure of Example 4, substituting a carrier having the formula



for the carrier. This dosing solution is designated as R-35B-DS.

Comparative Example 4C - Recombinant Human Growth Hormone Dosing Solutions

An intracolonic dosing solution was prepared according to the procedure of Example 4, substituting a carrier having the formula



for the carrier. This dosing solution is designated as R-9A-DS.

Example 5 - *In Vivo* Recombinant Human Growth Hormone Delivery

Male Sprague-Dawley rats weighing 200-250g were fasted for 24 hours and administered ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing. The rats were administered one of the dosing solutions of Example 3 by either oral gavage or intracolonic instillation. Blood samples were collected serially from the tail artery for determination of serum rHGH concentrations. Serum rHGH concentrations were quantified by an rHGH immunoassay test kit.

Results are illustrated in Table 3, below.

Comparative Example 5A - *In Vivo* Recombinant Human Growth Hormone Delivery

The procedure of Example 5 was followed, substituting the dosing solutions of Comparative Examples 3A-3C for the dosing solutions.
Results are illustrated in Table 3, below.

Comparative Example 5B - *In Vivo* Recombinant Human Growth Hormone Delivery

The procedure of Example 5 was followed, with dosing solutions of active agent (at a dose of 1 mg of rHGH/kg (intracolonic) or 3 mg of rHGH/kg (oral) and no carrier. These dosing solutions are designated R-ØD-DS and R-ØE-DS, respectively. Results are illustrated in Table 3, below.

TABLE 3 - *In Vivo* Recombinant Human Growth Hormone Delivery	
Dosing Solution	Mean Peak Serum [rHGH] ± Standard Deviation (ng/ml)
R-9-DS	125 ± 34 (IC)
R-35-DS	41 ± 46 (PO) 108 ± 56 (IC)
R-36-DS	28 ± 11 (IC)
R-47-DS	0 (IC)
R-62-DS	11 ± 12 (IC)
R-64-DS	72 ± 22 (PO)
R-67-DS	19 ± 22 (PO) 88 ± 24 (IC)
R-77-DS	34 ± 10 (PO)
R-79-DS	62 ± 51 (PO)
R-90-DS	9 ± 13 (PO)
R-94-DS	39 ± 35 (PO)
R-107-DS	0 ± 0 (PO)
R-109-DS	128 ± 25 (IC)
R-1●9-DS	106 ± 72 (IC)
R-141-DS	95 ± 14 (IC)
R-35A-DS	17 ± 3 (IC)
R-35B-DS	42 ± 28 (IC)
R-9A-DS	55 ± 17 (IC)
R-ØD-DS	0 ± 0 (IC)
R-ØE-DS	0 ± 0 (IC)

Example 6 - *In Vivo* Interferon Delivery

An intracolonic dosing composition containing 50 mg/kg of carrier 9 and 250 μg/kg of interferon in 50% propylene glycol was prepared. Rats were

administered the dosing composition by intracolonic instillation. Delivery was evaluated by use of an ELISA assay for human interferon *α* from Biosource, Inc. Mean peak serum interferon concentration was 2611 ± 695.

Comparative Example 6A - *In Vivo* Interferon Delivery

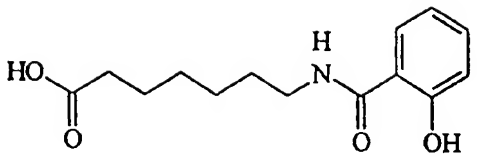
Rats were administered, orally and by intracolonic instillation, dosing solutions of 1 mg/kg of interferon and no carrier. Delivery was evaluated according to the procedure of Example 6. Mean peak serum interferon concentration was 1951 ± 1857 (PO) and 79 ± 100 (IC).

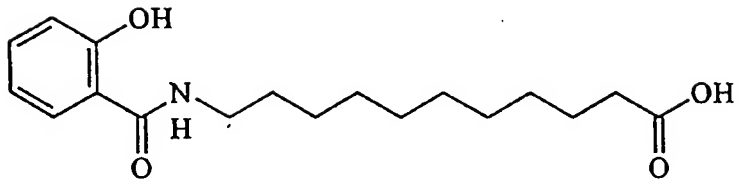
Example 7 - Heparin Dosing Solutions

Intracolonic dosing compositions containing 50 mg/kg of carrier and 25 mg/kg of heparin in 25% aqueous propylene glycol or oral gavage dosing solutions containing 300 mg/kg of carrier and 100 mg/kg of heparin in 25% aqueous propylene glycol were prepared with carriers 9, 35, 47, 50, 58, 62, 64, 67, 76, 96, 102, 109, 110, 111, 117, 122, 123, 139, 141, 144, and 169. The dosing solutions are designated H-carrier number-DS.

Comparative Example 7A - Heparin Dosing Solutions

Comparative intracolonic dosing compositions were prepared according to the procedure of Example 7, substituting the following carriers for the carrier.





These dosing solutions are designated H-35A-DS, H-35B-DS, and H-109A-DS, respectively.

Examples 8 - *In Vivo* Evaluation of Heparin in Rats

The dosing solutions of Example 7 were administered to fasted rats either by oral gavage or intracolonic instillation.

Blood samples were collected by cardiac puncture following the administration of ketamine (44 mg/kg). Heparin activity was determined by utilizing the activated partial thromboplastin time (APTT) according to the method of Henry, J.B., Clinical Diagnosis and Management by Laboratory Methods; Philadelphia, PA; W.B. Saunders (1979).

Results are in illustrated in Table 4, below.

Comparative Examples 8A - *In Vivo* Evaluation of Heparin in Rats

The dosing solutions of Comparative Example 7A were administered to fasted rats by intracolonic instillation. Blood samples were collected and heparin activity was determined by the method of Example 8.

Results are illustrated in Table 4, below.

Comparative Example 8B - *In Vivo* Evaluation of Heparin in Rats

An intracolonic dosing solution of 25 mg/kg of heparin and an oral gavage dosing solution of 100 mg/kg of heparin were administered to fasted rats. These dosage solutions were designated H-ØA-DS and H-ØB-DS, respectively.

Blood samples were collected, and heparin activity was determined by the methods of Example 8.

Results are illustrated in Table 4, below.

TABLE 4 - *In Vivo* Evaluation of Heparin in Rats	
Dosing Solution	Heparin APTT (sec)
H-9-DS	48 ± 18 (IC)
H-35-DS	54 ± 27 (PO), 177 ± 85 (IC)
H-47-DS	30 ± 14 (IC)
H-50-DS	40 ± 22 (IC)
H-58-DS	24 ± 4 (IC)
H-62-DS	37 ± 13 (IC)
H-64-DS	59 ± 28 (PO), 168 ± 75 (IC)
H-67-DS	76 ± 36 (IC)
H-76-DS	63 ± 27 (PO)
H-96-DS	36 ± 8 (IC)
H-102-DS	111 ± 108 (IC)
H-109-DS	56 ± 28 (IC)
H-110-DS	37 ± 9 (IC)
H-111-DS	71 ± 39 (IC)
H-117-DS	140 ± 128 (IC)
H-122-DS	49 ± 21 (IC), 207 ± 7 (PO)
H-123-DS	42 ± 14 (PO)
H-139-DS	31 ± 11 (IC)
H-141-DS	59 ± 26 (IC)
H-144-DS	26 ± 3 (IC)
H-35A-DS	61 ± 29 (IC)
H-35B-DS	51 ± 30 (IC)
H-169-DS	23 ± 2 (IC)
H-ØA-DS	23 ± 2 (PO)
H-ØB-DS	33 ± 6 (IC)

The above mentioned patents, applications, test methods, and publications are hereby incorporated by reference in their entirety.

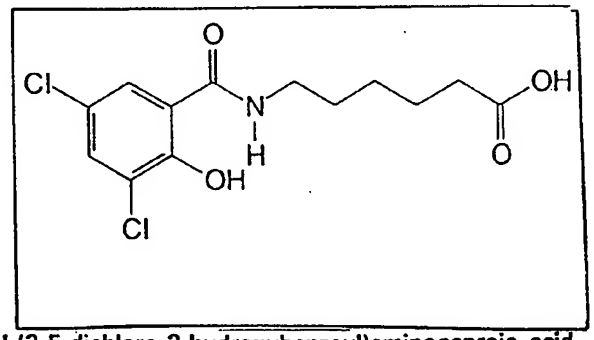
Many variations of the present invention will suggest themselves to those skilled in the art in light of the above detailed description. All such obvious variations are within the full intended scope of the appended claims.

WHAT IS CLAIMED IS:

1. A composition comprising:

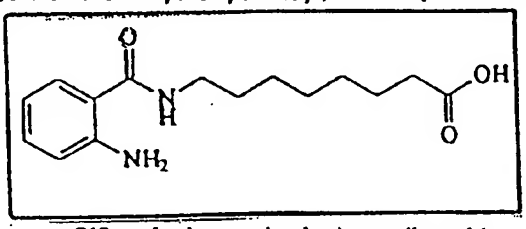
(A) at least one active agent; and

(B) at least one carrier selected from the group consisting of



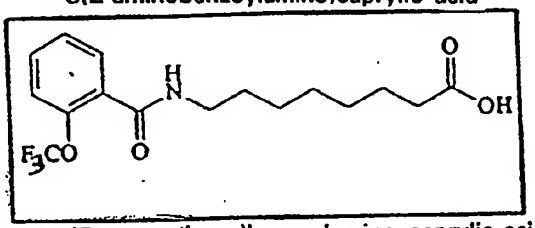
1

6-N-(3,5-dichloro-2-hydroxybenzoyl)aminocaproic acid



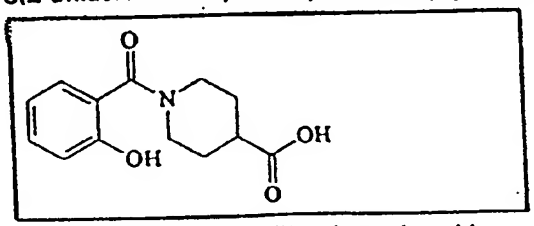
2

8(2-aminobenzoylamino)caprylic acid



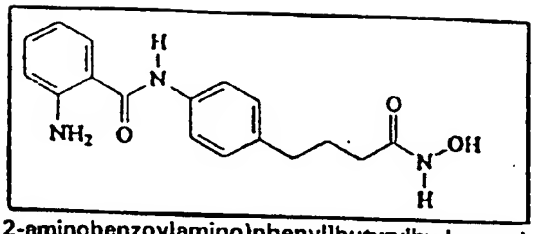
3

8(2-trifluoromethoxy)benzoylamino caprylic acid



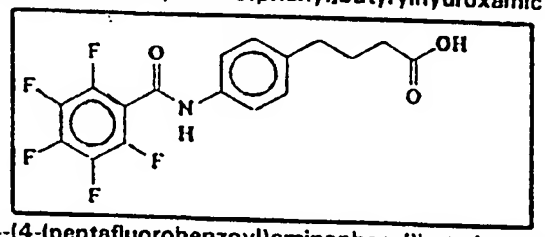
4

N-(2-hydroxybenzoyl)isonipecotic acid



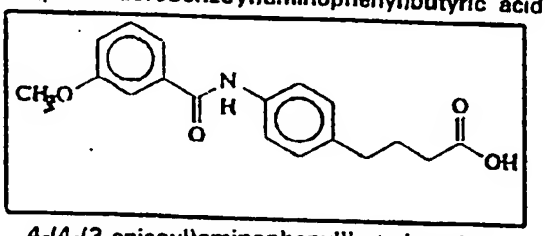
5

4-[4-(2-aminobenzoylamino)phenyl]butyrylhydroxamic acid



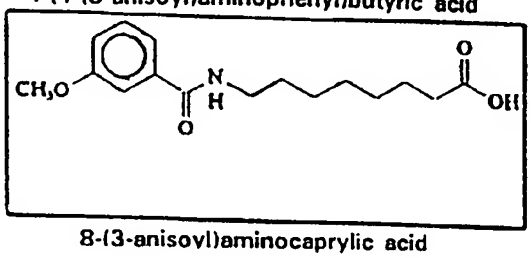
6

4-(4-(pentafluorobenzoyl)aminophenyl)butyric acid



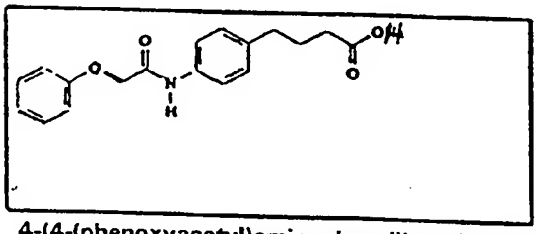
7

4-(4-(3-anisoyl)aminophenyl)butyric acid



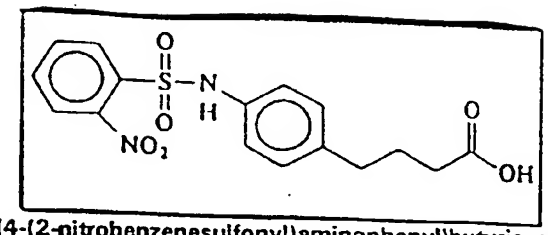
8

8-(3-anisoyl)aminocaprylic acid



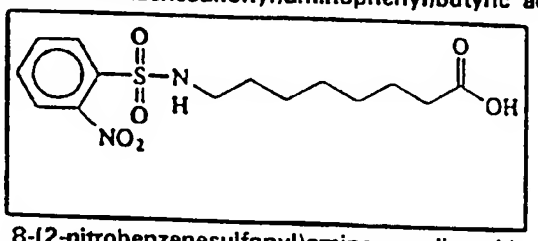
9

4-(4-(phenoxyacetyl)aminophenyl)butyric acid



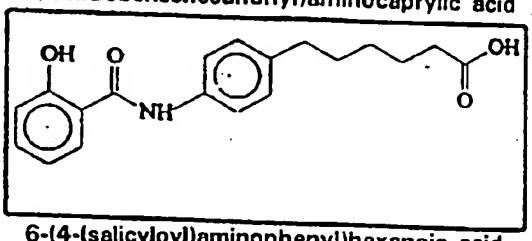
10

4-(4-(2-nitrobenzenesulfonyl)aminophenyl)butyric acid



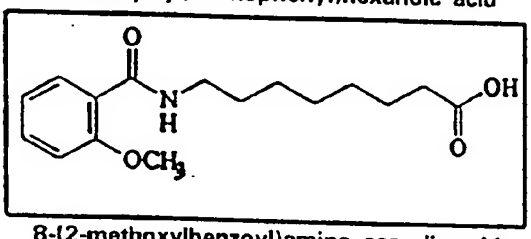
11

8-(2-nitrobenzenesulfonyl)aminocaprylic acid



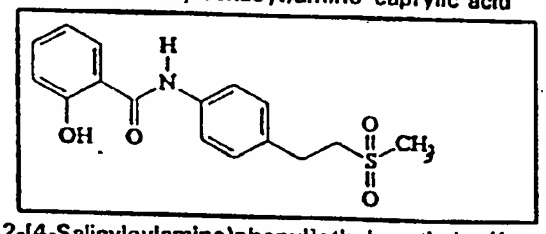
12

6-(4-(salicyloyl)aminophenyl)hexanoic acid



13

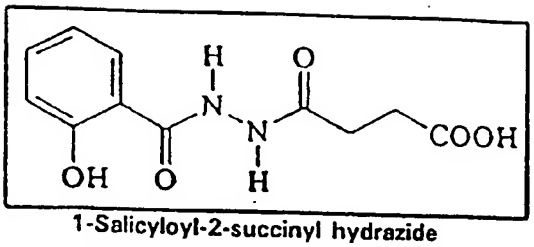
8-(2-methoxylbenzoyl)amino caprylic acid



14

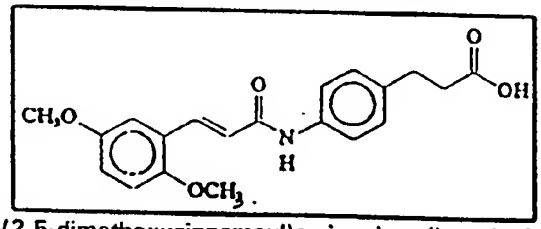
2-(4-Salicyloylamino)phenyl)ethyl methyl sulfone

15



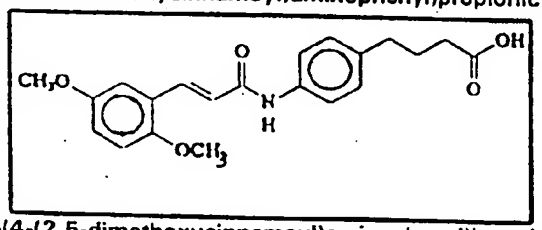
1-Salicyloyl-2-succinyl hydrazide

16



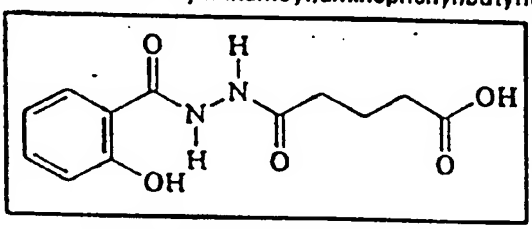
3-(4-(2,5-dimethoxycinnamoyl)aminophenyl)propionic acid

17

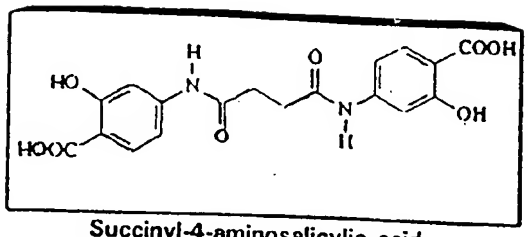


4-(4-(2,5-dimethoxycinnamoyl)aminophenyl)butyric acid

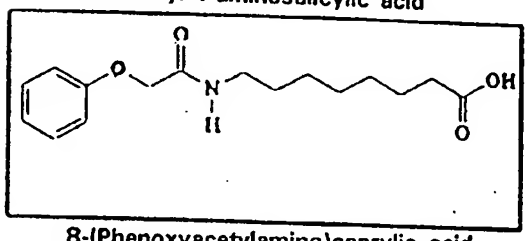
18



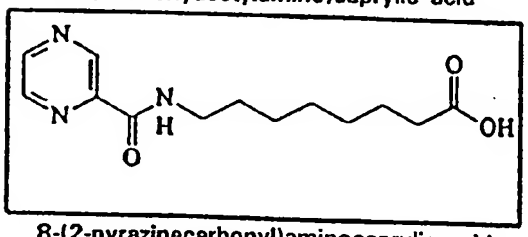
1-salicyloyl-2-glutaryl hydrazide



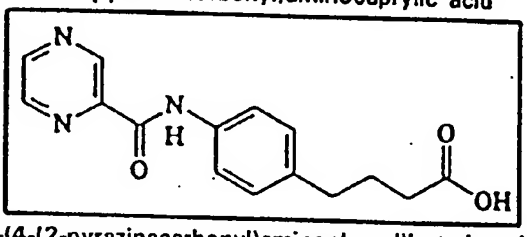
Succinyl-4-aminosalicylic acid 19



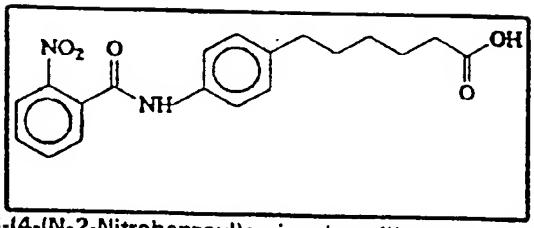
8-(Phenoxyacetylamino)caprylic acid 20



8-(2-pyrazinecarbonyl)aminocaprylic acid 21

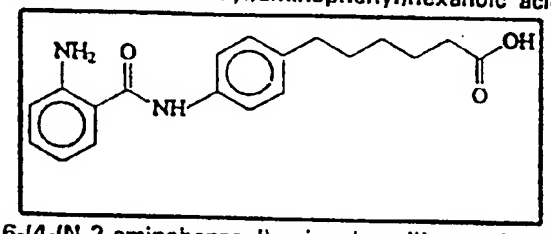


4-(4-(2-pyrazinecarbonyl)aminophenyl)butyric acid 22



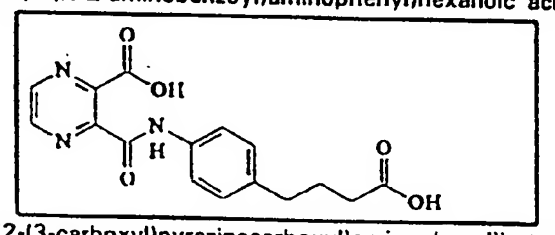
23

6-(4-(N-2-Nitrobenzoyl)aminophenyl)hexanoic acid



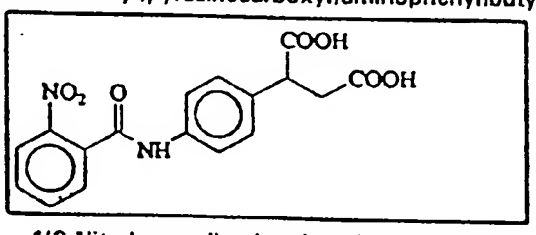
24

6-(4-(N-2-aminobenzoyl)aminophenyl)hexanoic acid



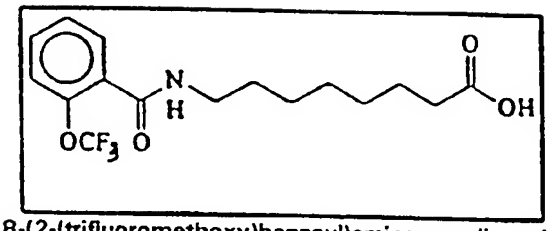
25

4-(4-(2-(3-carboxyl)pyrazinecarboxyl)aminophenyl)butyric acid



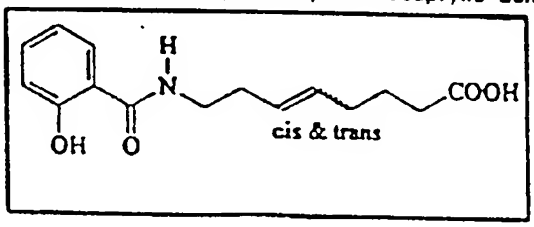
26

4(2-Nitrobenzoyl)aminophenylsuccinic acid

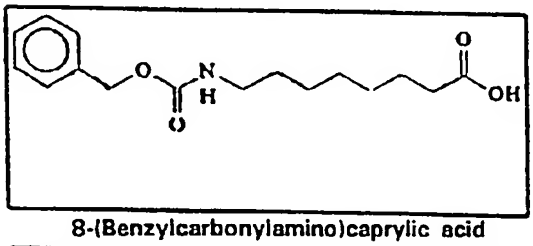


27

8-(2-(trifluoromethoxy)benzoyl)aminocaprylic acid

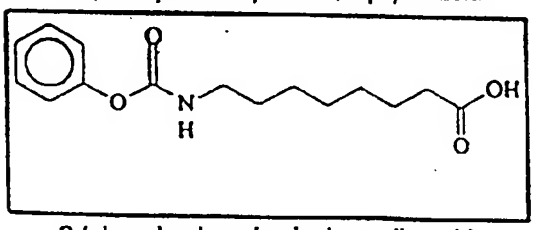


28



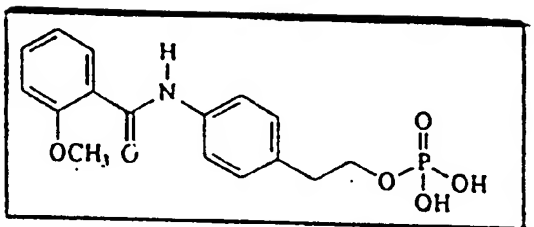
29

8-(Benzylcarbonylamino)caprylic acid



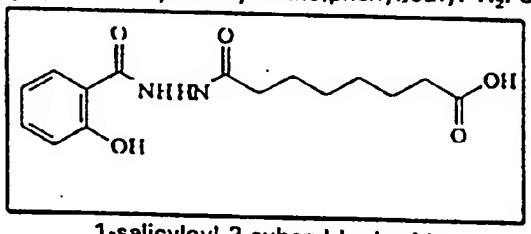
30

8-(phenylcarbonylamino)caprylic acid



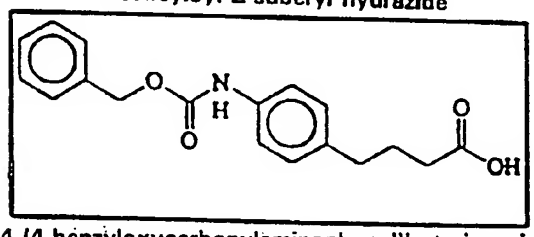
31

2-[4-(2-Methoxybenzoylamino)phenyl]ethyl H_2PO_4



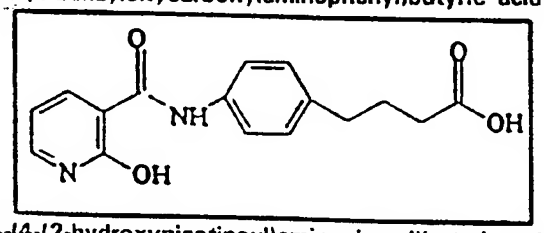
32

1-salicyloyl-2-suberyl hydrazide



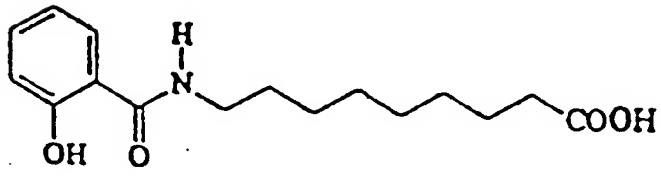
33

4-(4-benzyloxycarbonylaminophenyl)butyric acid

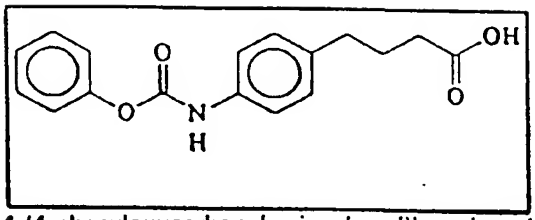


34

4-(4-(2-hydroxynicotinoyl)aminophenyl)butyric acid

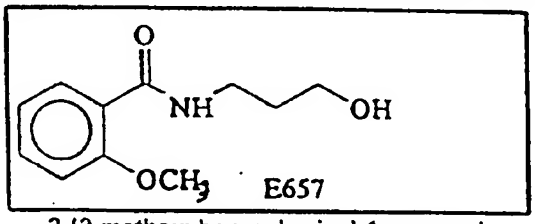


35



36

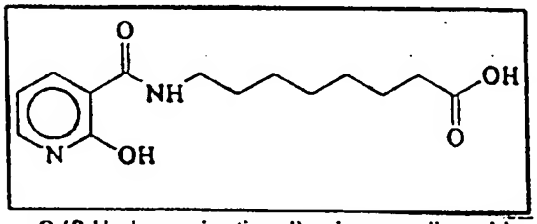
4-(4-phenyloxycarbonylaminophenyl)butyric acid



37

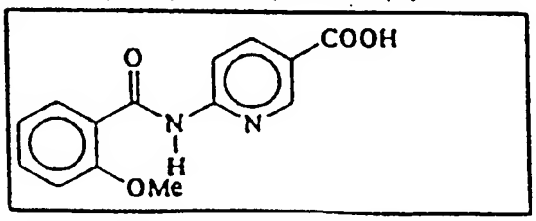
3-(2-methoxybenzoylamino)-1-propanol

E657



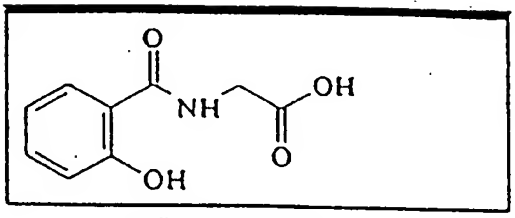
38

8-(2-Hydroxynicotinoyl)aminocaprylic acid



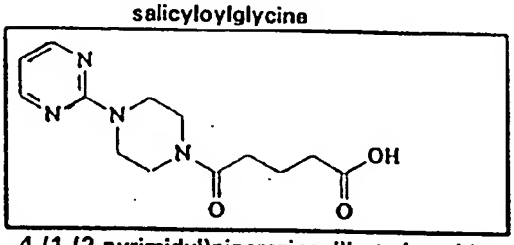
39

6-(2-methoxybenzoyl)amino nicotinic acid



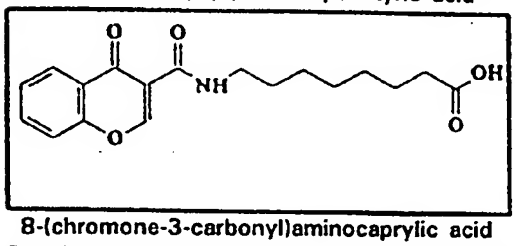
40

salicyloylglycine



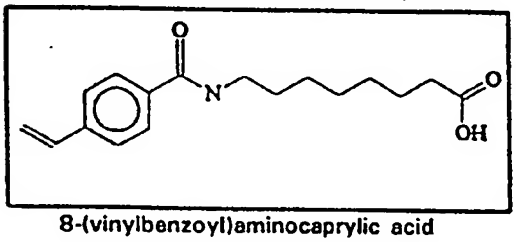
41

4-(1-(2-pyrimidyl)piperazinoyl)butyric acid



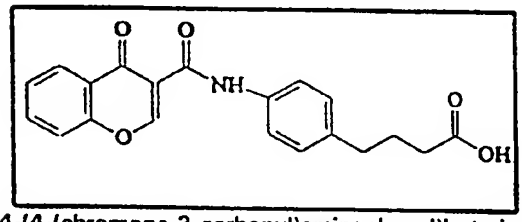
42

8-(chromone-3-carbonyl)aminocaprylic acid



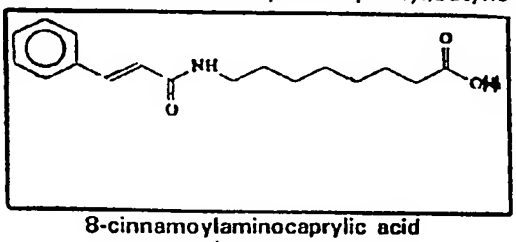
43

8-(vinylbenzoyl)aminocaprylic acid



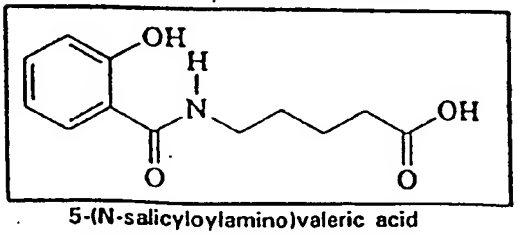
44

4-(4-(chromone-3-carbonyl)aminophenyl)butyric acid



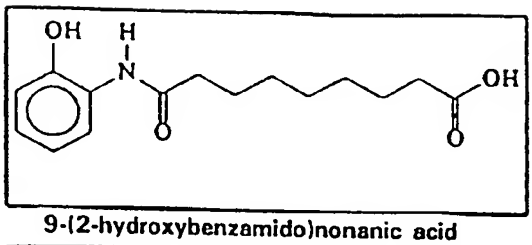
45

8-cinnamoylaminocaprylic acid



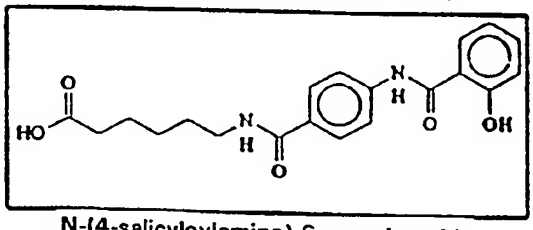
46

5-(N-salicyloylamino)valeric acid



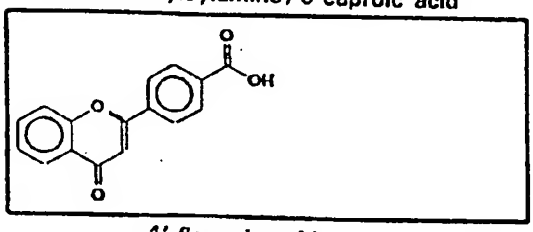
9-(2-hydroxybenzamido)nonanic acid

47



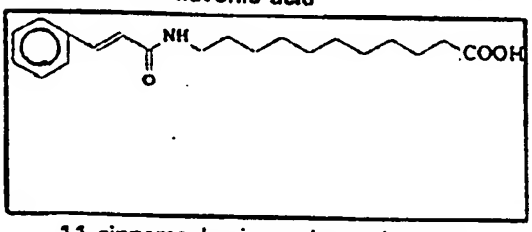
N-(4-salicyloylamino)-6-caproic acid

48



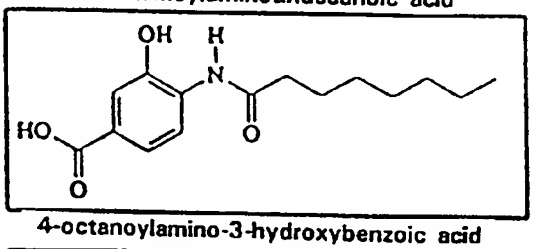
4'-flavonic acid

49



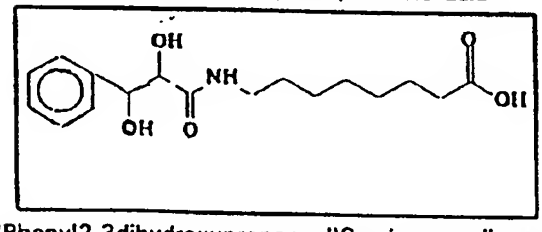
11-cinnamoylaminoundecanoic acid

50



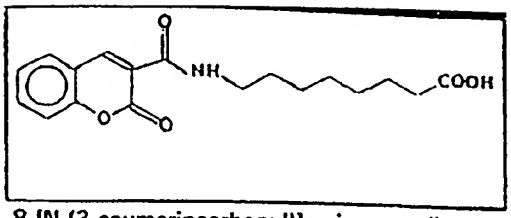
4-octanoylamino-3-hydroxybenzoic acid

51



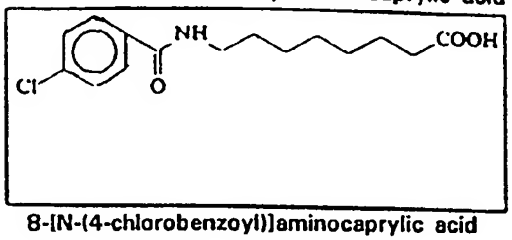
(3Phenyl2,3dihydroxypropanoyl)8aminocaprylic acid

52



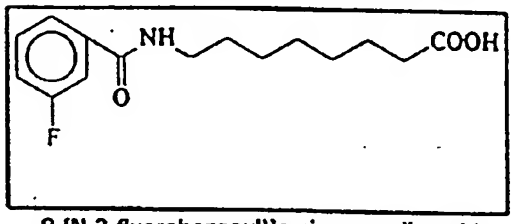
53

8-[N-(3-coumarincarbonyl)]aminocaprylic acid



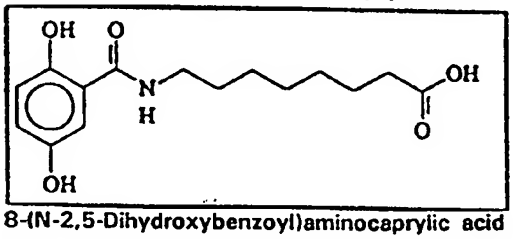
54

8-[N-(4-chlorobenzoyl)]aminocaprylic acid



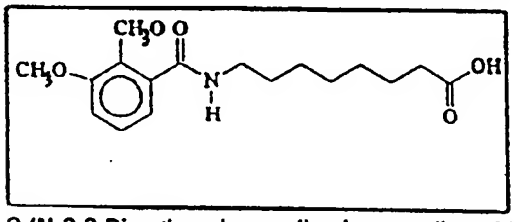
55

8-[N-3-fluorobenzoyl)]aminocaprylic acid



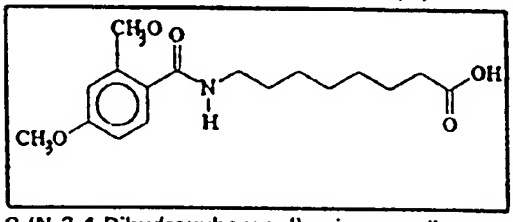
56

8-(N-2,5-Dihydroxybenzoyl)aminocaprylic acid



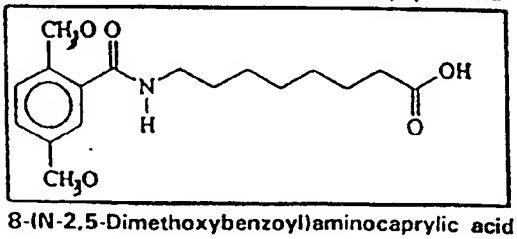
57

8-(N-2,3-Dimethoxybenzoyl)aminocaprylic acid



58

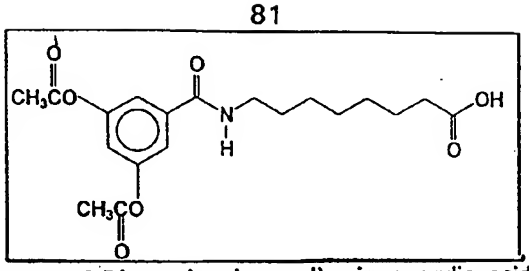
8-(N-2,4-Dihydroxybenzoyl)aminocaprylic acid



59

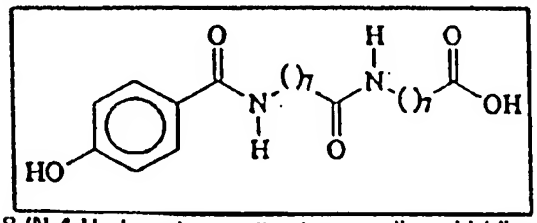
8-(N-2,5-Dimethoxybenzoyl)aminocaprylic acid

81



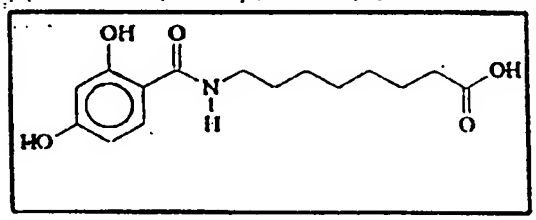
60

8-(N-3,5-Diacetyloxybenzoyl)aminocaprylic acid



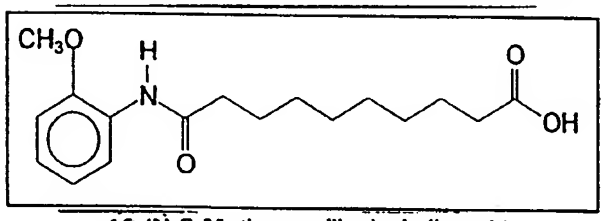
61

8-(N-4-Hydroxybenzoyl)aminocaprylic acid (dimer)



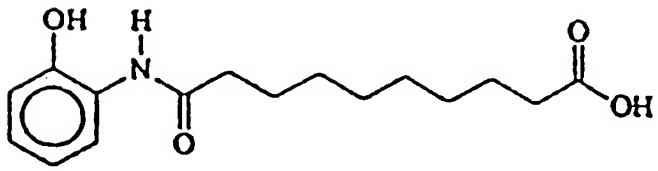
62

8-(N-2,4-Dihydroxybenzoyl)aminocaprylic acid

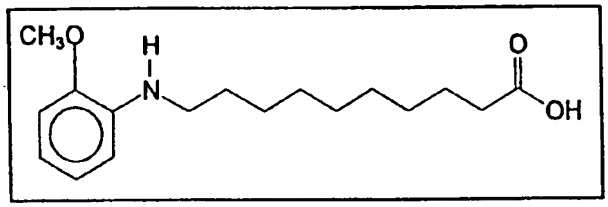


63

10-(N-2-Methoxyanilino)sebalic acid

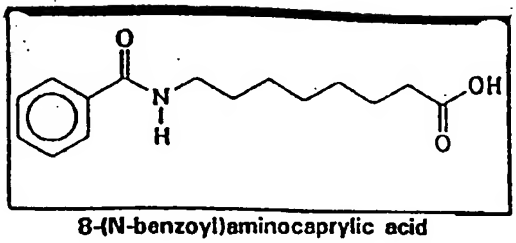


64



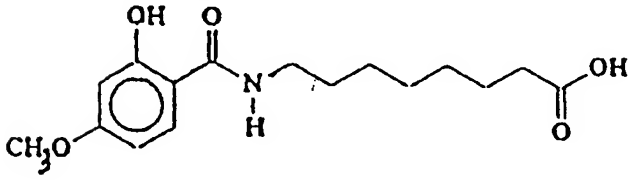
65

2-Methoxybenzenaminodecanoic acid

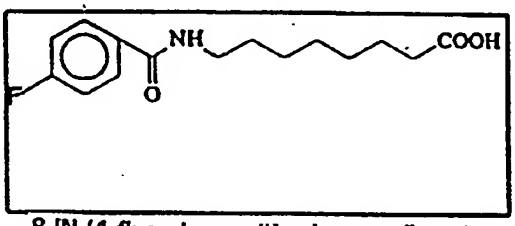


66

8-(N-benzoyl)aminocaprylic acid

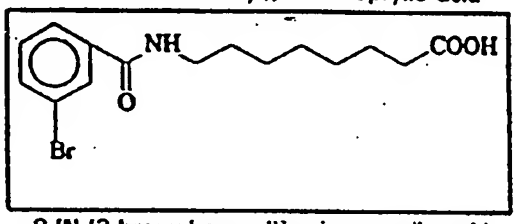


67



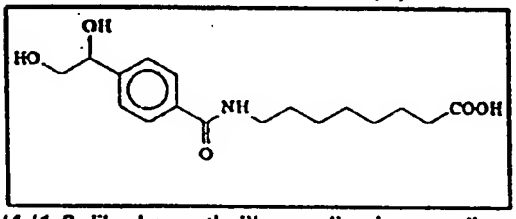
68

8-[N-(4-fluorobenzoyl)]aminocaprylic acid



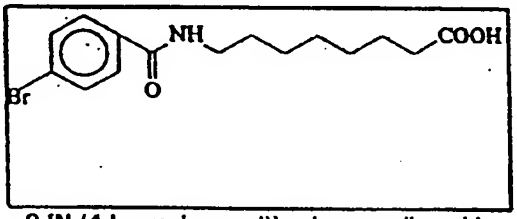
69

8-[N-(3-bromobenzoyl)]aminocaprylic acid



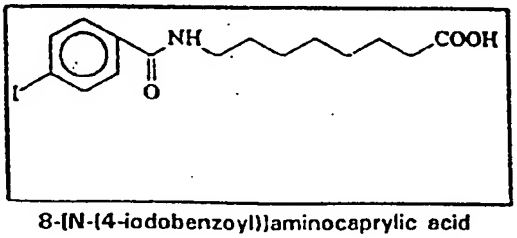
70

8-(4-(1,2-dihydroxyethyl)benzoyl)aminocaprylic acid



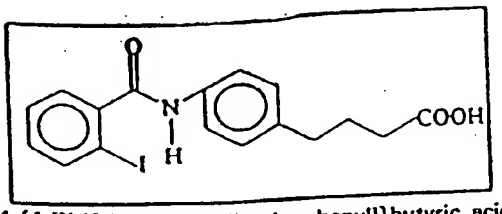
71

8-[N-(4-bromobenzoyl)]aminocaprylic acid



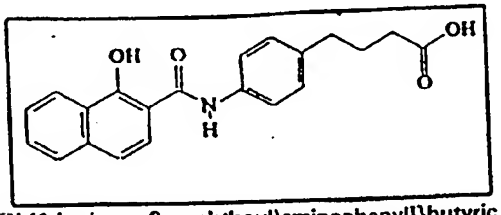
72

8-[N-(4-iodobenzoyl)]aminocaprylic acid



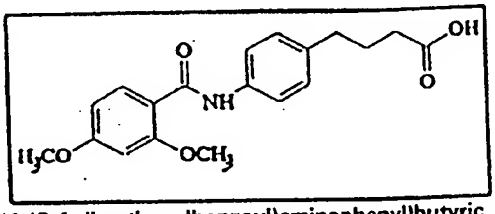
73

4-{4-[N-(2-iodobenzoyl)aminophenyl]}butyric acid



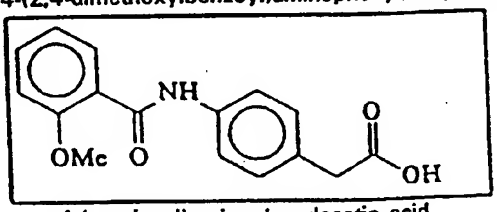
74

4-{4-[N-(1-hydroxy-2-naphthoyl)aminophenyl]}butyric acid



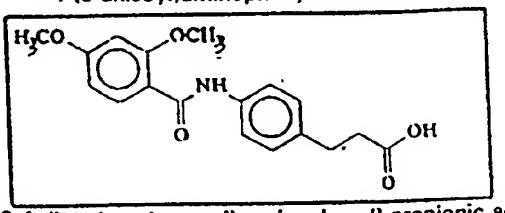
75

4-(4-(2,4-dimethoxylbenzoyl)aminophenyl)butyric acid



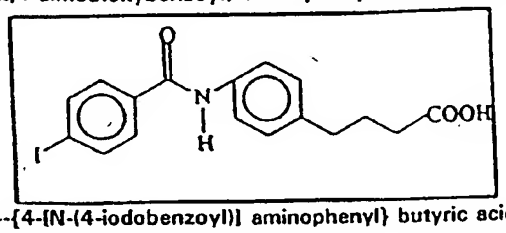
76

4-(o-anisoyl)aminophenylacetic acid



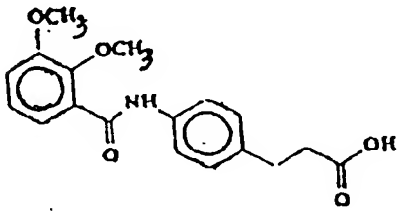
77

3-[4-(2,4-dimethoxybenzoyl) aminophenyl] propionic acid

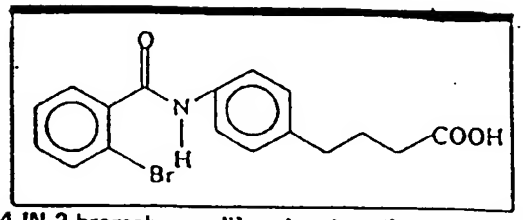


78

4-{4-[N-(4-iodobenzoyl)] aminophenyl} butyric acid

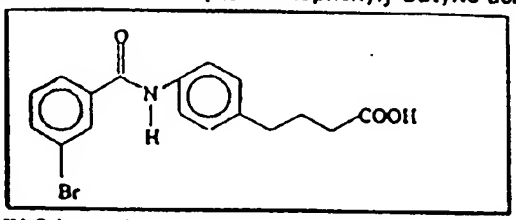


79



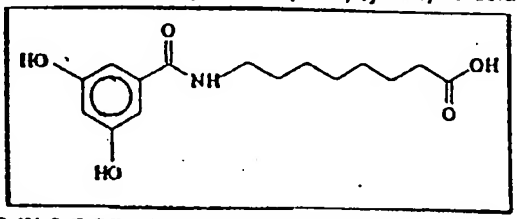
80

4{4-[N-2-bromobenzoyl)] aminophenyl} butyric acid



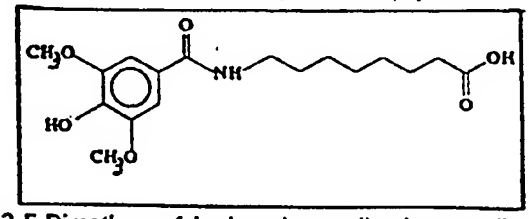
81

4{4-[N-3-bromobenzoyl) aminophenyl]} butyric acid



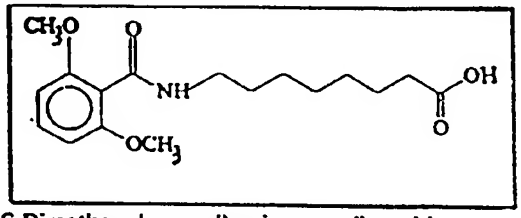
82

8-(N-3,5 Dihydroxybenzoyl)aminocaprylic acid



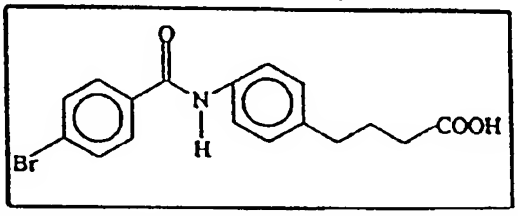
83

8-(N-3,5-Dimethoxy 4-hydroxybenzoyl)aminocaprylic acid



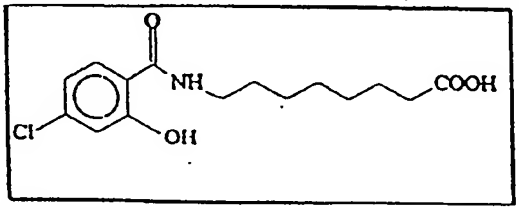
84

8-(N-2-6-Dimethoxybenzoyl)aminocaprylic acid



85

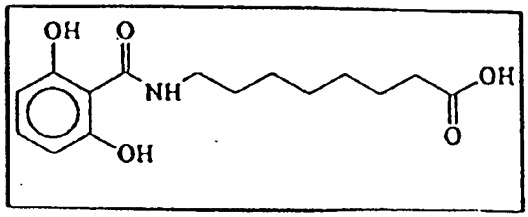
4-{4-[N-(4-bromobenzoyl)aminophenyl]}butyric acid



86

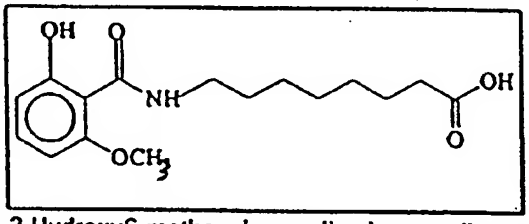
8-(2-hydroxy-4-chlorobenzoyl)aminocaprylic acid

87



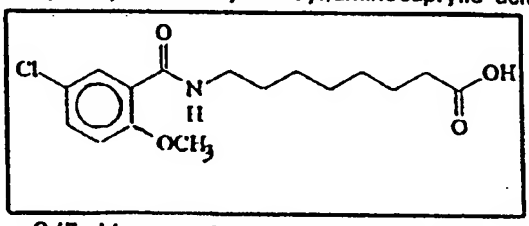
8-(N-2,6-Dihydroxybenzoyl)aminocaprylic acid

88



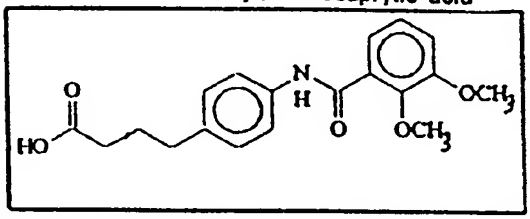
8-(N-2-Hydroxy6-methoxybenzoyl)aminocaprylic acid

89



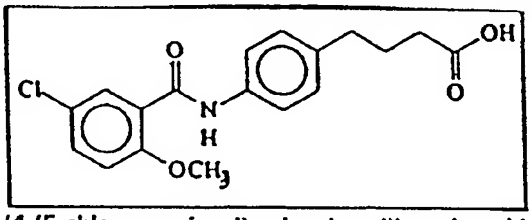
8-(5-chloro-o-anisoyl)aminocaprylic acid

90



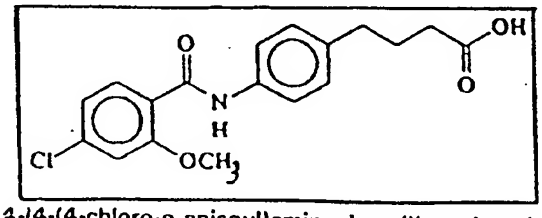
4-(4-(2,3-dimethoxybenzoyl)aminophenyl)butyric acid

91

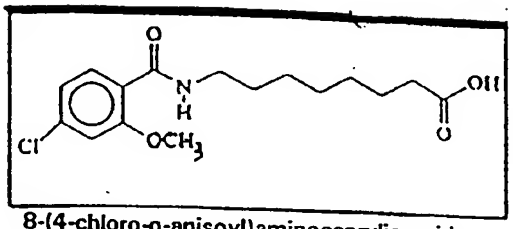


4-(4-(5-chloro-o-anisoyl)aminophenyl)butyric acid

92

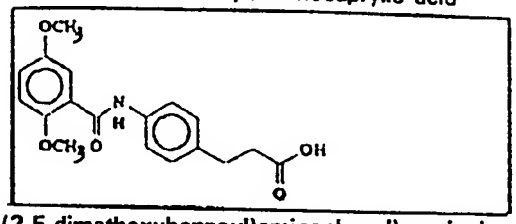


4-(4-(4-chloro-o-anisoyl)aminophenyl)butyric acid



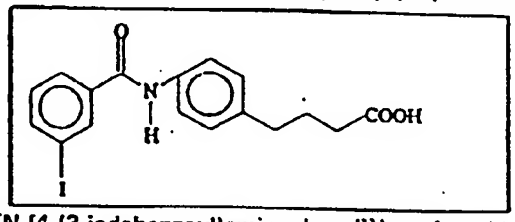
93

8-(4-chloro-o-anisoyl)aminocaprylic acid



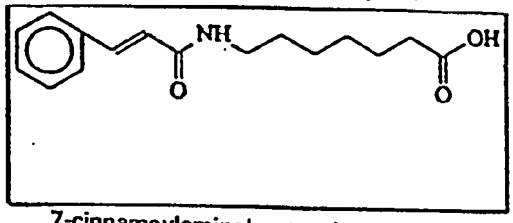
94

3-(4-(2,5-dimethoxybenzoyl)aminophenyl)propionic acid



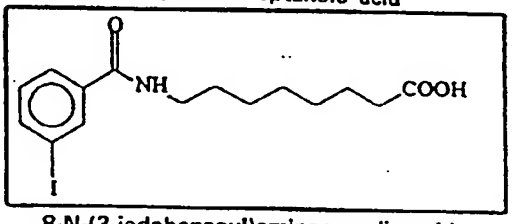
95

4-{N-[4-(3-iodobenzoyl)aminophenyl]}butyric acid



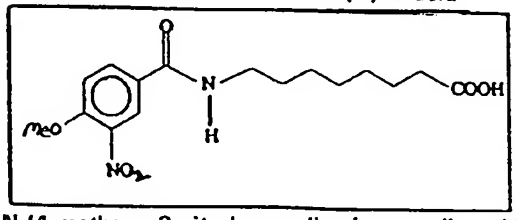
96

7-cinnamoylaminoheptanoic acid



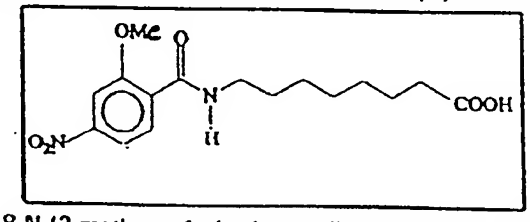
97

8-N-(3-iodobenzoyl)aminocaprylic acid



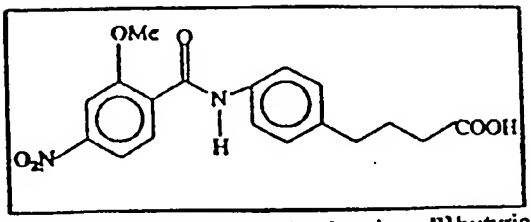
98

8-N-(4-methoxy-3-nitrobenzoyl)aminocaprylic acid



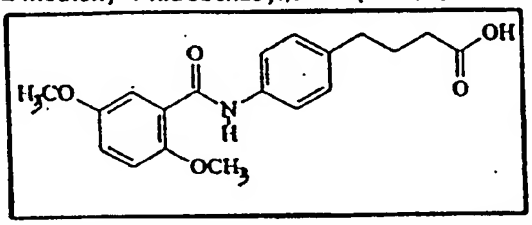
99

8-N-(2-methoxy-4-nitrobenzoyl)aminocaprylic acid



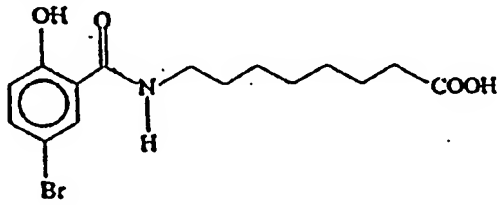
100

4-{N-[4-(2-methoxy-4-nitrobenzoyl)aminophenyl]}butyric acid

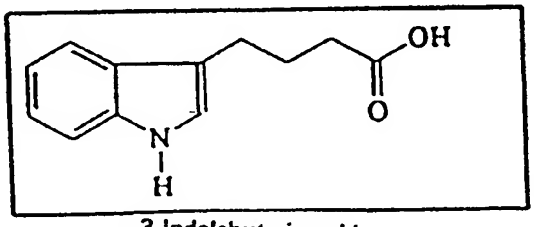


101

4-(4-(2,5-dimethoxybenzoyl)aminophenyl)butyric acid

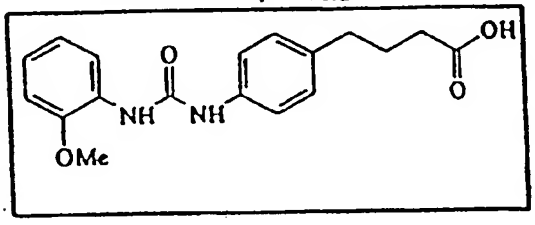


102

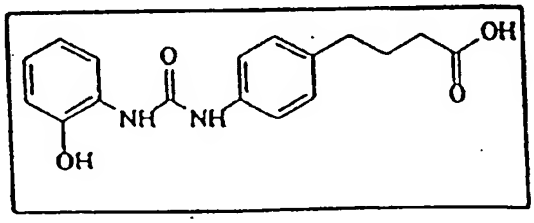


103

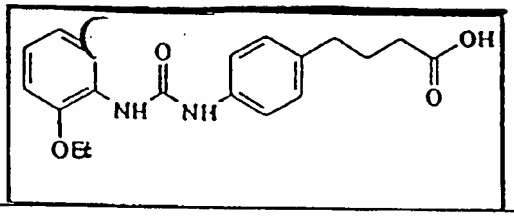
3-Indolebutyric acid



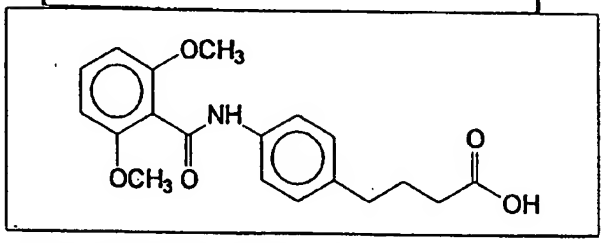
104



105

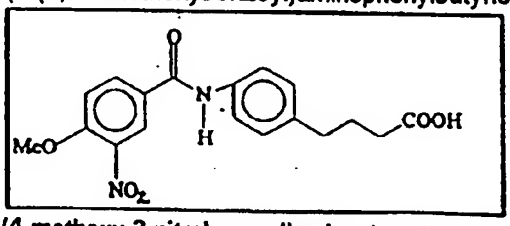


106



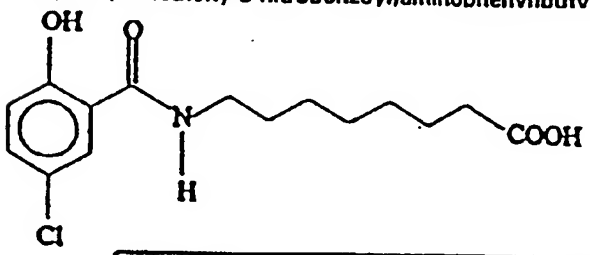
107

4-(4-(2,6-dimethoxybenzoyl)aminophenylbutyric acid

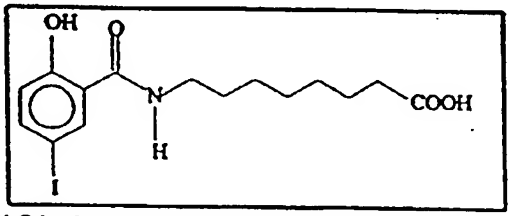


108

4-[4-N-(4-methoxy-3-nitrobenzoyl)aminophenyllbutyric acid

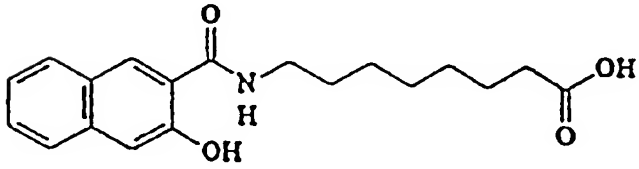


109

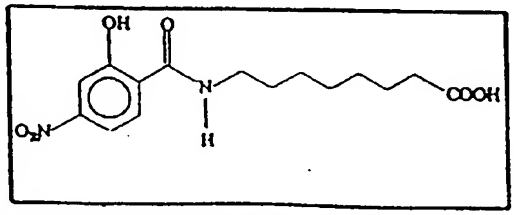


110

8-(N-2-hydroxy-5-iodobenzoyl)aminocaprylic acid

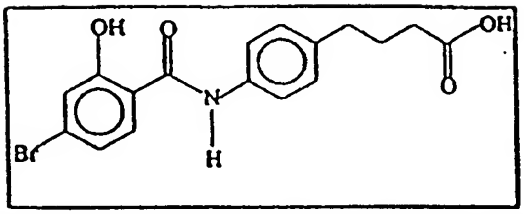


111



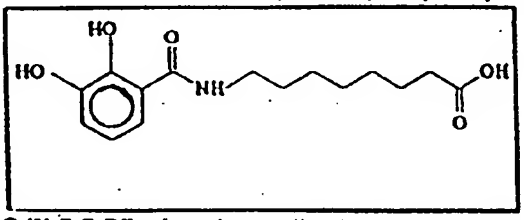
112

8-(N-2-hydroxy-4-nitrobenzoyl)aminocaprylic acid



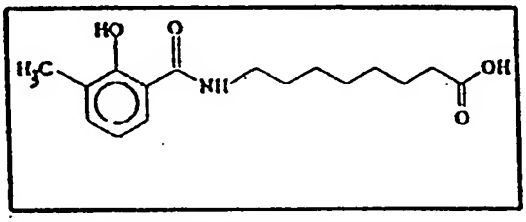
113

4-[-N-(2-hydroxy-4-bromobenzoyl)aminophenyl]butyric acid



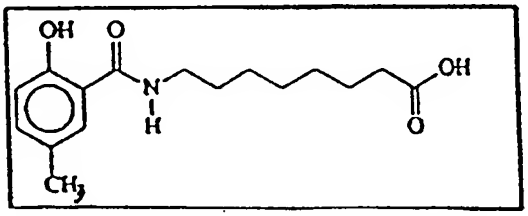
114

8-(N-2,3-Dihydroxybenzoyl)aminocaprylic acid



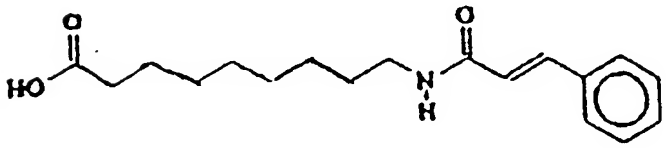
115

8-(N-3-methylsalicyloyl)aminocaprylic acid

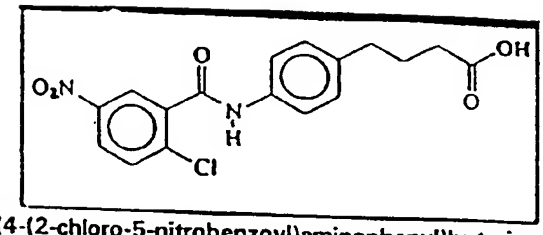


116

8-(N-5-methylsalicyloyl)aminocaprylic acid

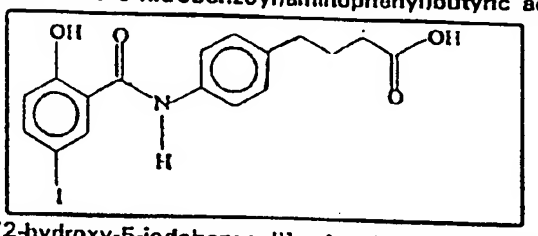


117



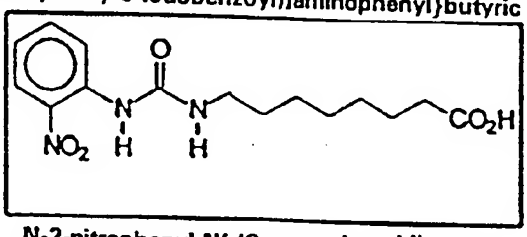
118

4-(4-(2-chloro-5-nitrobenzoyl)aminophenyl)butyric acid



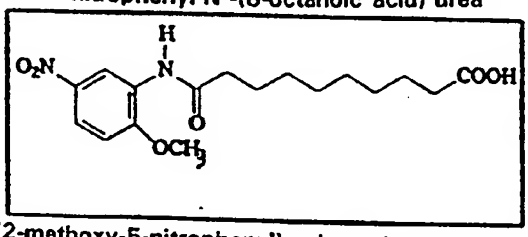
119

4-{-[N-(2-hydroxy-5-iodobenzoyl)]aminophenyl}butyric acid



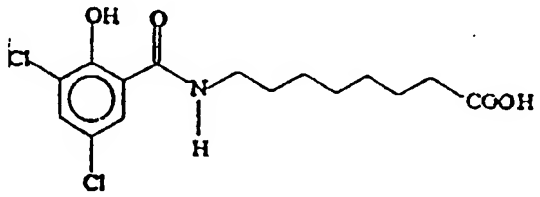
120

N-2-nitrophenyl-N'-(8-octanoic acid) urea

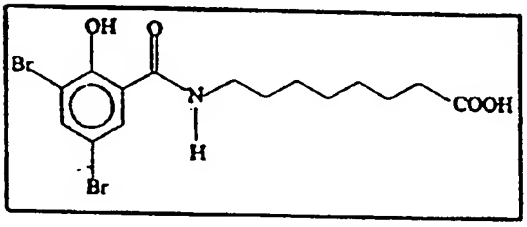


121

N-(2-methoxy-5-nitrophenyl) sebecoyl amide acid

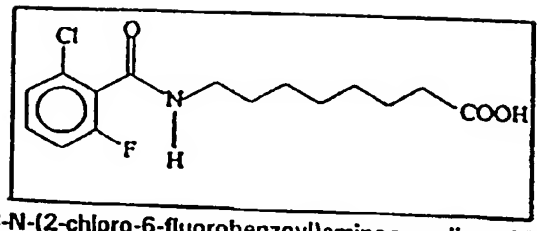


122



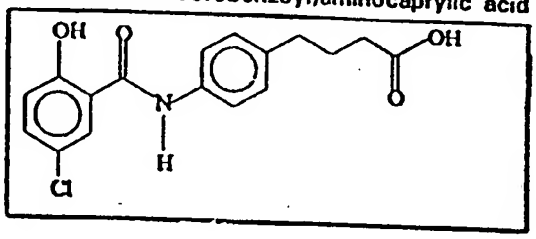
123

8-[N-(2-acetoxy-3,5-dibromobenzoyl)]aminocaprylic acid

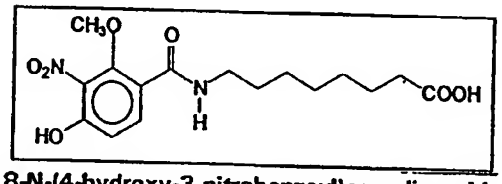


124

8-N-(2-chloro-6-fluorobenzoyl)aminocaprylic acid

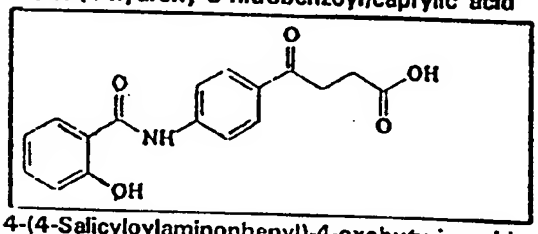


125



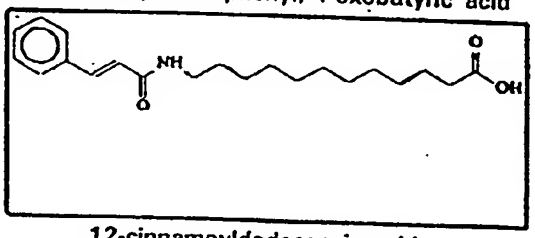
126

8-N-(4-hydroxy-3-nitrobenzoyl)caprylic acid



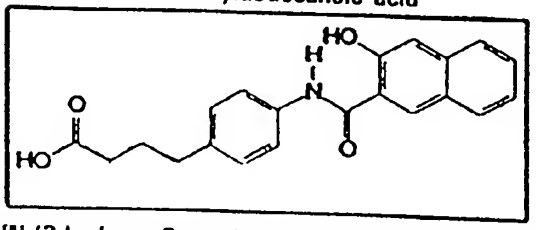
127

4-(4-Salicyloylaminophenyl)-4-oxobutyric acid



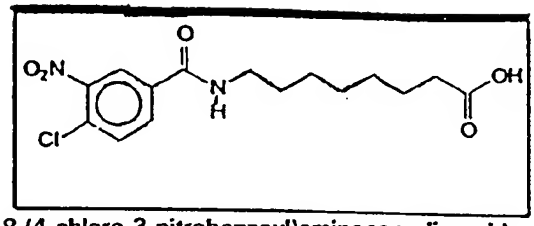
128

12-cinnamoyldodecanoic acid



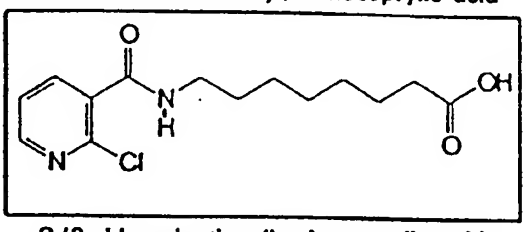
129

4-{4-[N-(3-hydroxy-2-napthoyl)aminophenyl]}butyric acid



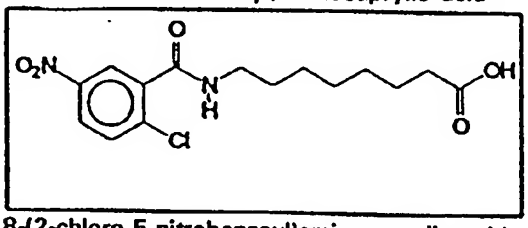
130

8-(4-chloro-3-nitrobenzoyl)aminocaprylic acid



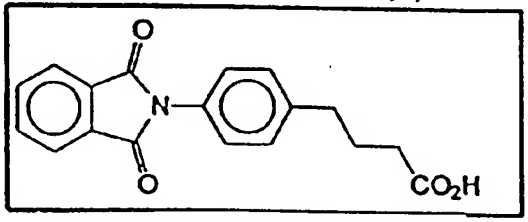
131

8-(2-chloronicotinoyl)aminocaprylic acid



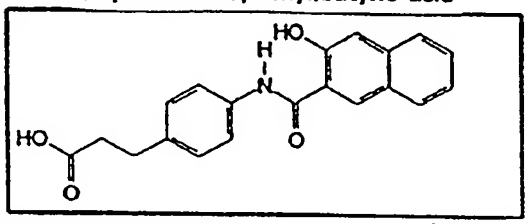
132

8-(2-chloro-5-nitrobenzoyl)aminocaprylic acid



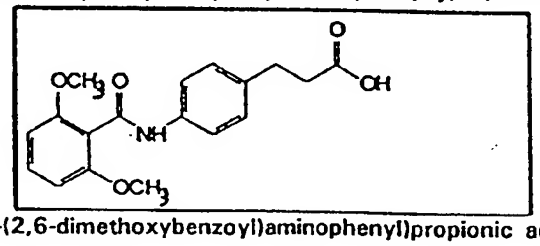
133

4-(4-phthalimidophenyl)butyric acid



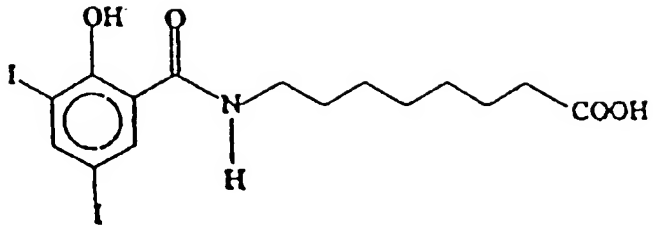
134

4-{4-[N-(3-hydroxy-2-napthoyl)aminophenyl]}propanoic acid

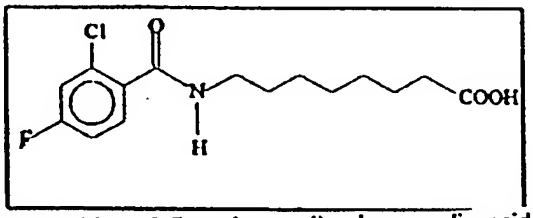


135

3-(4-(2,6-dimethoxybenzoyl)aminophenyl)propionic acid

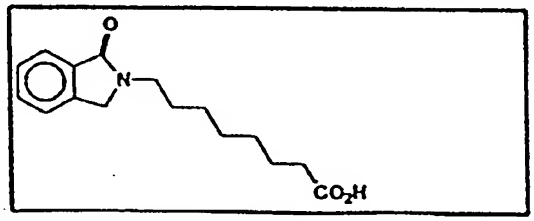


136



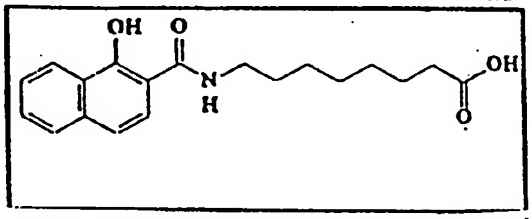
137

8-(N-2-chloro-4-fluorobenzoyl)aminocaprylic acid



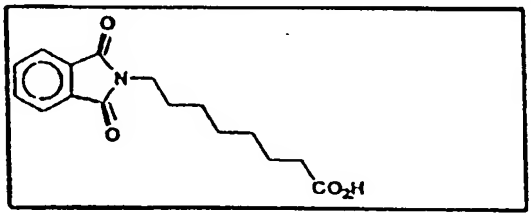
138

8-(2-(1,2-dihydroisoindole-1-one))octanoic acid



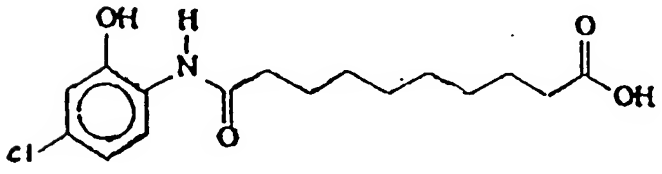
139

8-(N-1-hydroxy-2-naphthoyl)aminocaprylic acid

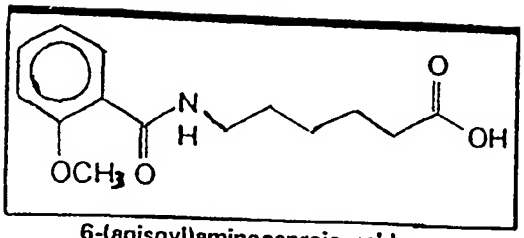


140

8-(phthalimido)caprylic acid

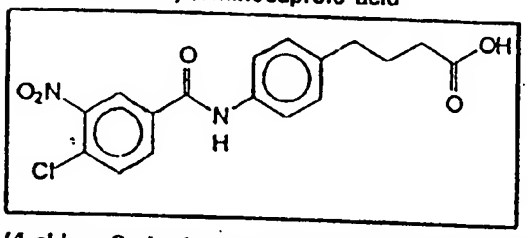


141



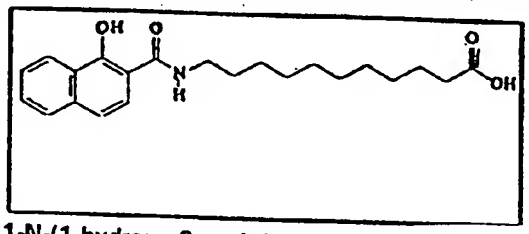
142

6-(anisoyl)aminocaproic acid



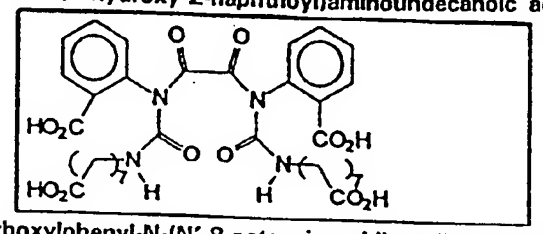
143

4-(4-(4-chloro-3-nitrobenzoyl)aminophenyl)butyric acid



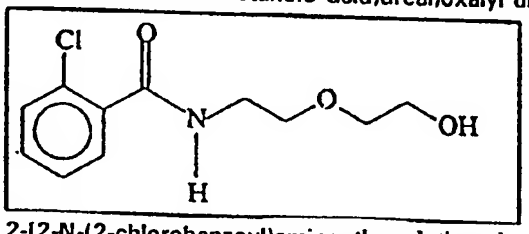
144

11-N-(1-hydroxy-2-naphthoyl)aminoundecanoic acid



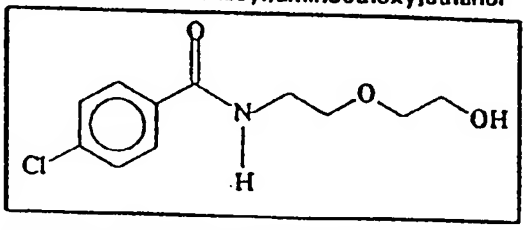
145

Bis(N-2carboxylphenyl-N-(N'-8-octanoic acid)ureal)oxalyl diamide



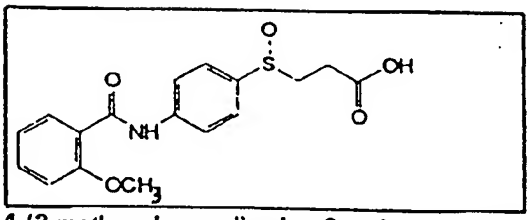
146

2-[2-N-(2-chlorobenzoyl)aminoethoxy]ethanol



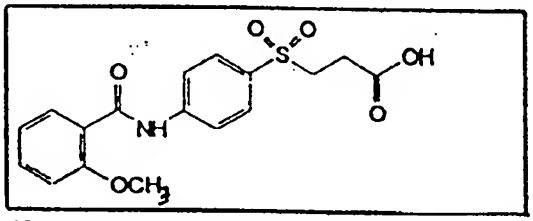
147

2-[2-N-(4-chlorobenzoyl)aminoethoxy]ethanol



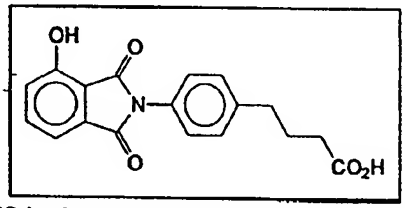
148

4-(2-methoxybenzoyl)amino 3-carboxysulfoxide



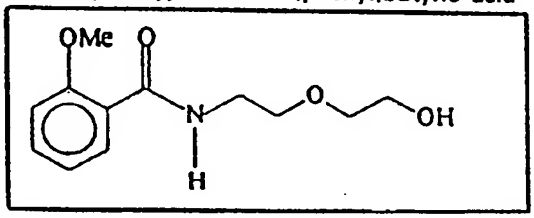
149

4-(2-methoxybenzoyl)amino 3-carboxypropylsulfone



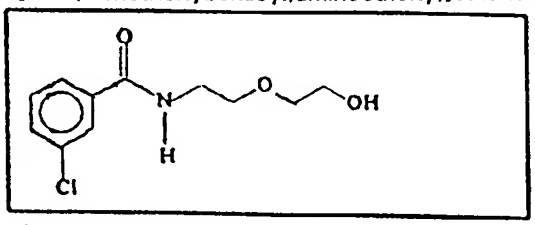
150

4-(4-(3-hydroxyphthalimido)phenyl)butyric acid



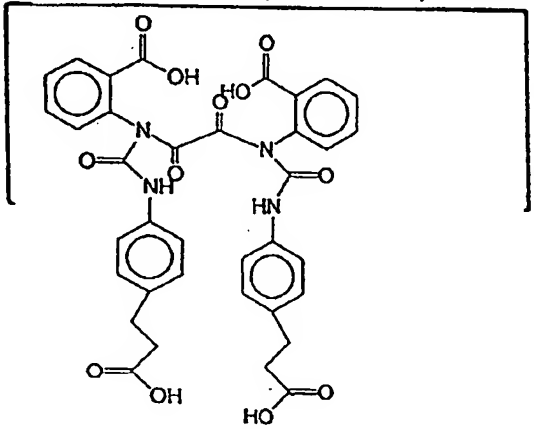
151

2-[2-N-(2-methoxybenzoyl)aminoethoxy)]ethanol



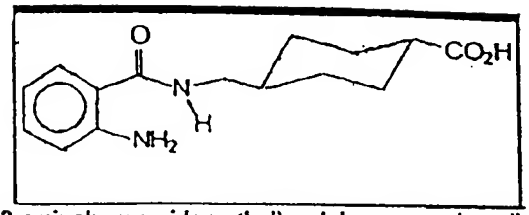
152

2-[2-N-(3-chlorobenzoyl)aminoethoxy)]ethanol



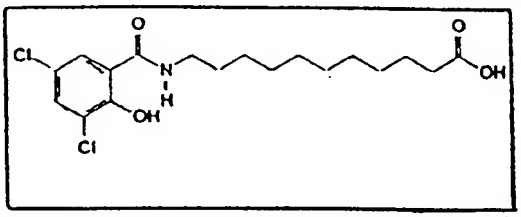
153

Bis(N-2-carboxyphenyl-N-(N'-3(4-aminophenyl)propionic acid)ureal)oxaylyl diamide



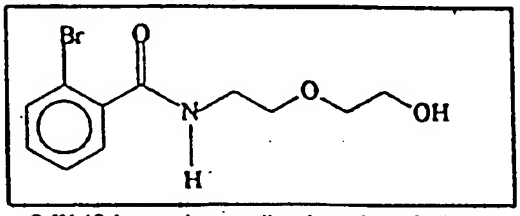
154

trans-4-(2-aminobenzamidomethyl)cyclohexamecarboxylic acid



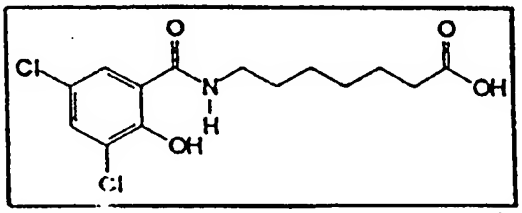
155

11-N-(3,5-dichloro-2-hydroxybenzoyl)aminoundecanoic acid



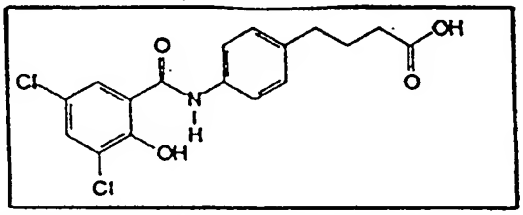
156

2-[N-(2-bromobenzoyl)aminoethoxy]ethanol



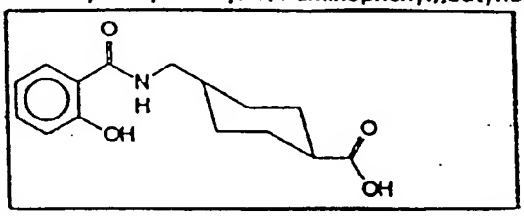
157

7-N-(3,5-dichloro-2-hydroxybenzoyl)aminoheptanoic acid



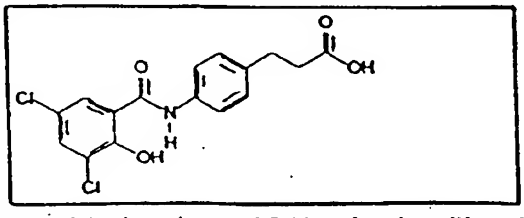
158

N-[3,5-dichloro-2-hydroxybenzoyl-4(4-aminophenyl)]butyric acid



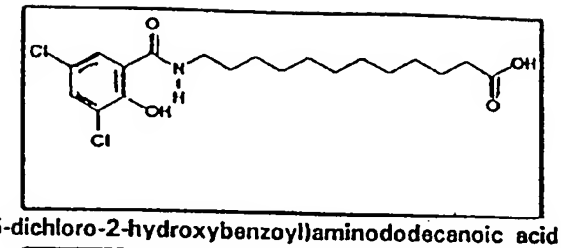
159

trans-4-(N-salicyloylaminomethyl)cyclohexane carboxylic acid



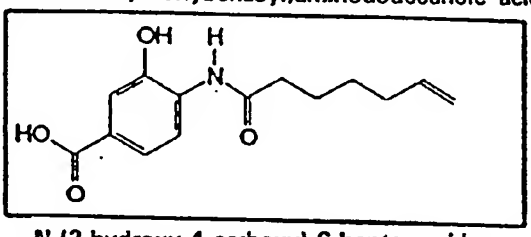
160

N-[3,5-dichloro-2-hydroxybenzoyl-3-(4-aminophenyl)]propionic acid



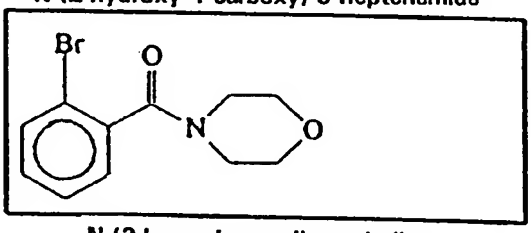
161

12-N-(3,5-dichloro-2-hydroxybenzoyl)aminododecanoic acid



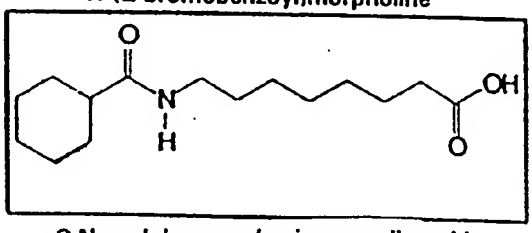
162

N-(2-hydroxy-4-carboxy)-6-heptenamide



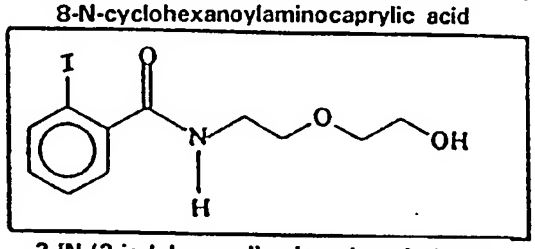
163

N-(2-bromobenzoyl)morpholine



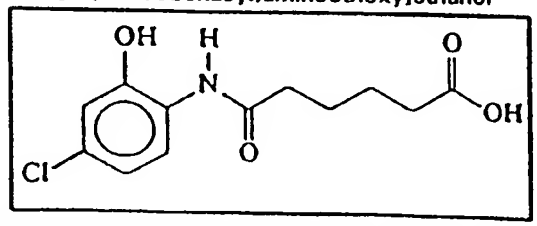
164

8-N-cyclohexanoylaminocaprylic acid



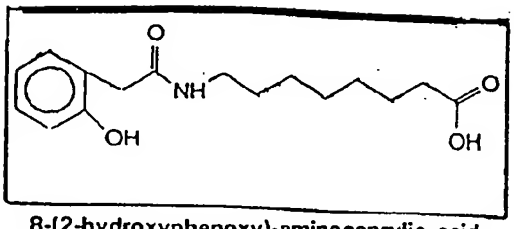
165

2-[N-(2-iodobenzoyl)aminoethoxy]ethanol



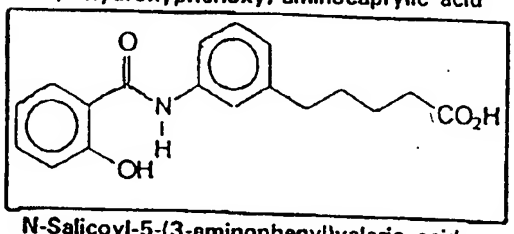
166

5-(4-chloro-2-hydroxyanilinocarbonyl)valeric acid



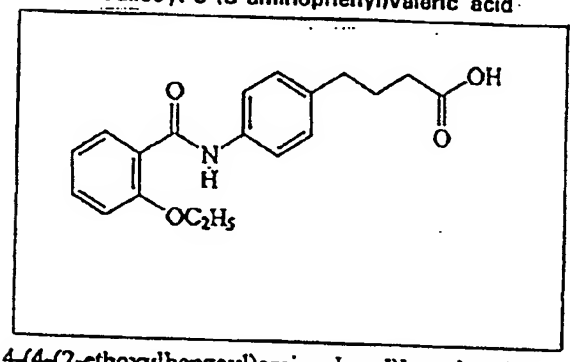
167

8-(2-hydroxyphenoxy)-aminocaprylic acid



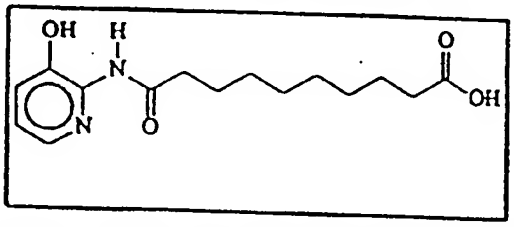
168

N-Salicoyl-5-(3-aminophenyl)valeric acid



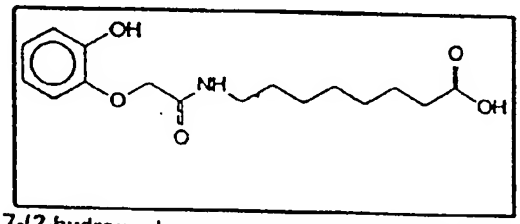
169

4-(4-(2-ethoxylbenzoyl)aminophenyl)butyric acid



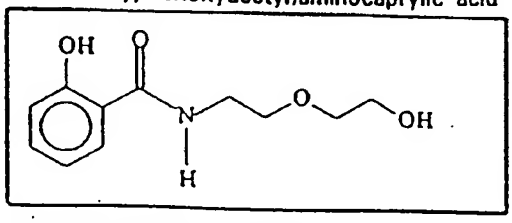
170

9-[2-(3-hydroxy)pyridylaminocarbonyl] nonanic acid



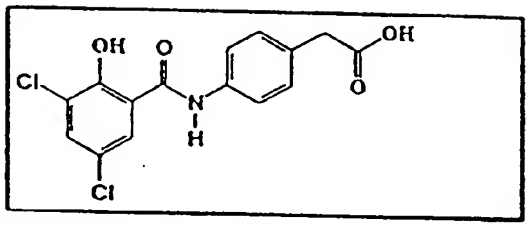
171

7-(2-hydroxyphenoxyacetyl)aminocaprylic acid



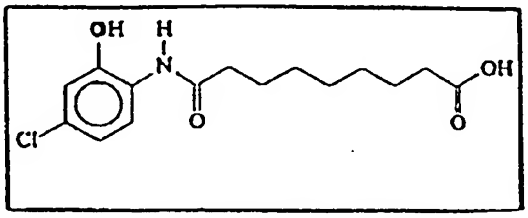
172

2-[N-(2-hydroxybenzoylamino)ethoxy]ethanol



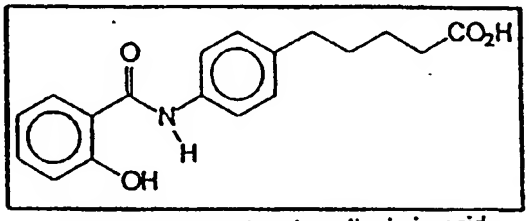
173

4-[N-(3,5-dichloro-2-hydroxybenzoyl)]aminophenylacetic acid



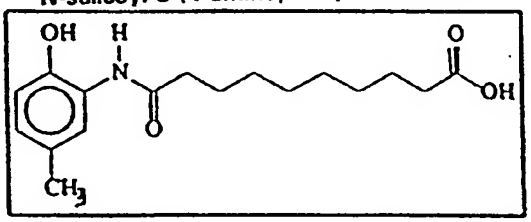
174

8-(2-hydroxy-5-chloroanilinocarbonyl)octanoic acid



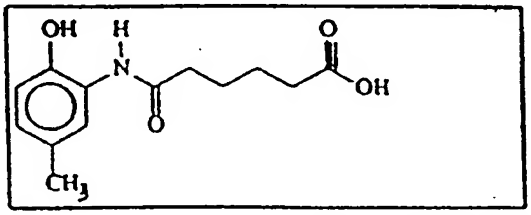
175

N-salicoyl-5-(4-aminophenyl)valeric acid



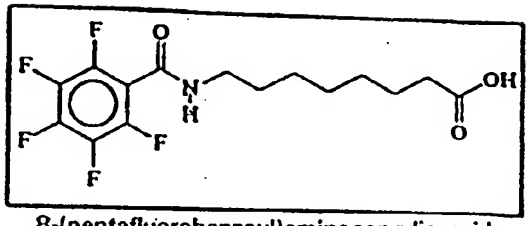
176

9-(2-hydroxy-5-methylanilinocarbonyl)nonanoic acid



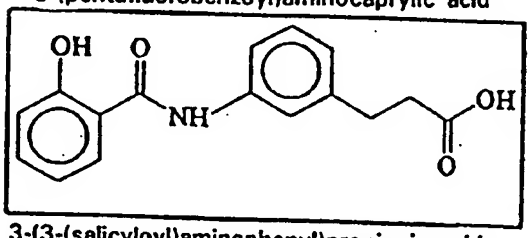
177

5-(2-hydroxy-5-methylanilinocarbonyl)valeric acid



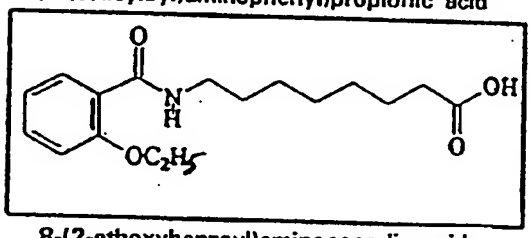
178

8-(pentafluorobenzoyl)aminocaprylic acid



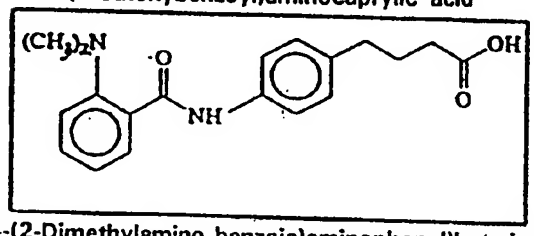
179

3-(3-(salicyloyl)aminophenyl)propionic acid



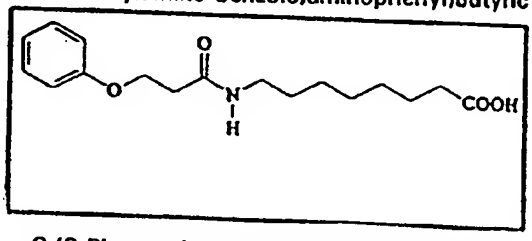
180

8-(2-ethoxybenzoyl)aminocaprylic acid



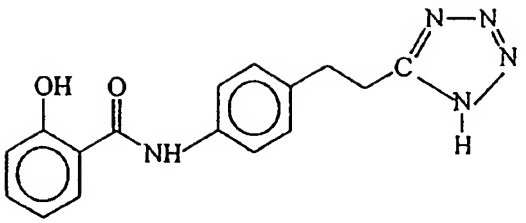
181

4-(4-(2-Dimethylamino benzoic)aminophenyl)butyric acid



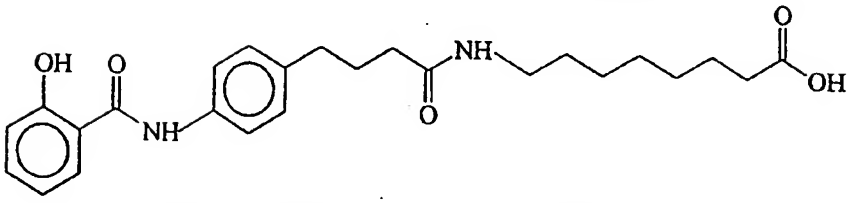
182

8-(3-Phenoxylpropionylamino)caprylic acid



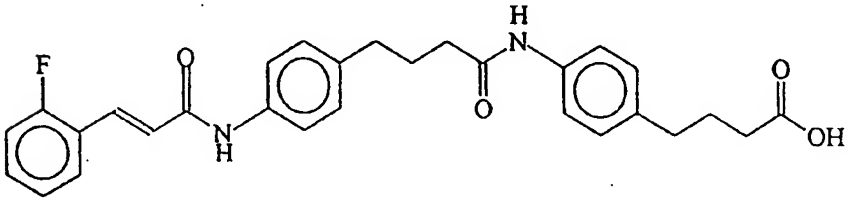
183

4-(Salicyloyl)aminophenylethyltetrazole



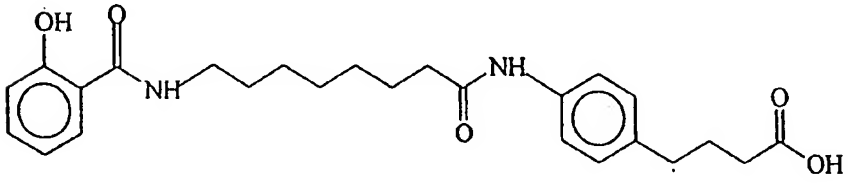
184

8(-(4(N-Saliciloyl-4aminophenyl)butyric)aminocaprylic acid [sic]



185

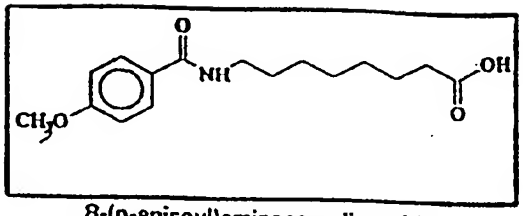
4-(4-(N-(2-Fluorocinnamoyl))aminophenyl) butyric



186

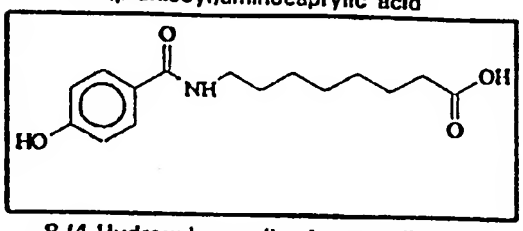
4-(4-(N-8(N-Salicyloyl)aminocaprylic)aminophenyl)butyric acid

187



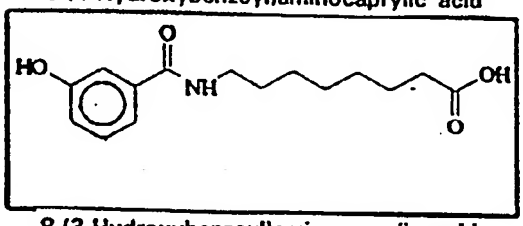
8-(p-anisoyl)aminocaprylic acid

188



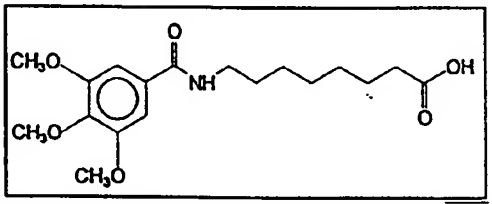
8-(4-Hydroxybenzoyl)aminocaprylic acid

189



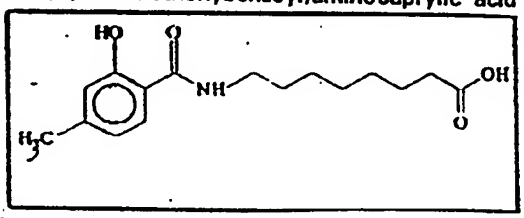
8-(3-Hydroxybenzoyl)aminocaprylic acid

190



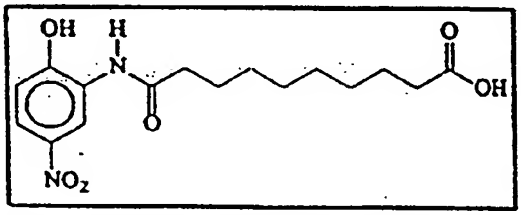
8-(3,4,5-Trimethoxybenzoyl)aminocaprylic acid

191



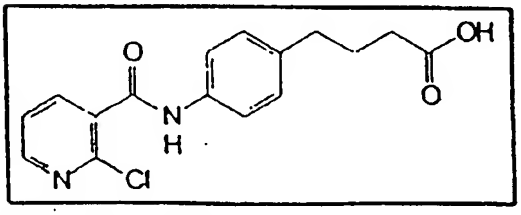
8-(N-4-Methylsalicyloyl)aminocaprillic acid [sic]

192



N-10-(2-hydroxy-5-nitroanilino)decanoic acid

193



4-(4-(2-chloronicotinoyl)aminophenyl)butyric acid

and a salt of any of the foregoing.

2. A composition as defined in claim 1, wherein said active agent is selected from the group consisting of a biologically active agent, a chemically active agent, or a combination thereof.

3. A composition as defined in claim 2, wherein said biologically active agent comprises at least one peptide, mucopolysaccharide, carbohydrate, or lipid.

4. A composition as defined in claim 2, wherein said biologically active agent is selected from the group consisting of human growth hormone, bovine growth hormone, growth hormone-releasing hormone, an interferon, interleukin-II, insulin, heparin, low molecular weight heparin, calcitonin, erythropoietin, atrial naturetic factor, an antigen, a monoclonal antibody, samatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium, vancomycin, parathyroid hormone, desferrioxamine (DFO), or any combination thereof.

5. A composition as defined in claim 4, wherein said biologically active agent comprises an interferon, interleukin-II, insulin, heparin, low molecular weight heparin, calcitonin, oxytosin, vasopressin, vancomycin, DFO, parathyroid hormone, and combinations thereof.

6. A composition as defined in claim 1, wherein said carrier comprises a poly(amino acid).

7. A composition as defined in claim 1, wherein said carrier comprises a polypeptide.

8. A dosage unit form comprising

(A) a composition as defined in claim 1; and

(B) (a) an excipient

(b) a diluent,

(c) a disintegrant,

(d) a lubricant,

(e) a plasticizer,

(f) a colorant,

(g) a dosing vehicle, or

(h) any combination thereof.

9. A composition as defined in claim 8, wherein said active agent is selected from the group consisting of a biologically active agent, a chemically active agent, or a combination thereof.

10. A composition as defined in claim 9, wherein said biologically active agent comprises at least one peptide, mucopolysaccharide, carbohydrate, or lipid.

11. A composition as defined in claim 9, wherein said biologically active agent is selected from the group consisting of human growth hormone, bovine growth hormone, growth hormone-releasing hormone, an interferon, interleukin-II, insulin, heparin, low molecular weight heparin, calcitonin, erythropoietin, atrial naturetic factor, an antigen, a monoclonal antibody, samatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium, vancomycin, parathyroid hormone, desferrioxamine (DFO), or any combination thereof.

12. A composition as defined in claim 11, wherein said biologically active agent comprises an interferon, interleukin-II, insulin, heparin, low molecular

weight heparin, calcitonin, oxytosin, vasopressin, vancomycin, DFO, parathyroid hormone, and combinations thereof.

13. A dosage unit form comprising

(A) a composition as defined in claim 6; and

(B) (a) an excipient

(b) a diluent,

(c) a disintegrant,

(d) a lubricant,

(e) a plasticizer,

(f) a colorant,

(g) a dosing vehicle, or

(h) any combination thereof.

14. A composition as defined in claim 13, wherein said active agent is selected from the group consisting of a biologically active agent, a chemically active agent, or a combination thereof.

15. A composition as defined in claim 14, wherein said biologically active agent comprises at least one peptide, mucopolysaccharide, carbohydrate, or lipid.

16. A composition as defined in claim 14, wherein said biologically active agent is selected from the group consisting of human growth hormone, bovine growth hormone, growth hormone-releasing hormone, an interferon, interleukin-II, insulin, heparin, low molecular weight heparin, calcitonin, erythropoietin, atrial naturetic factor, an antigen, a monoclonal antibody, samatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium, vancomycin, parathyroid hormone, desferrioxamine (DFO), or any combination thereof.

17. A composition as defined in claim 16, wherein said biologically active agent comprises an interferon, interleukin-II, insulin, heparin, low molecular weight heparin, calcitonin, oxytosin, vasopressin, vancomycin, DFO, parathyroid hormone, and combinations thereof.

18. A dosage unit form comprising

(A) a composition as defined in claim 7; and

(B) (a) an excipient

(b) a diluent,

(c) a disintegrant,

(d) a lubricant,

(e) a plasticizer,

(f) a colorant,

(g) a dosing vehicle, or

(h) any combination thereof.

19. A composition as defined in claim 18, wherein said active agent is selected from the group consisting of a biologically active agent, a chemically active agent, or a combination thereof.

20. A composition as defined in claim 19, wherein said biologically active agent comprises at least one peptide, mucopolysaccharide, carbohydrate, or lipid.

21. A composition as defined in claim 19, wherein said biologically active agent is selected from the group consisting of human growth hormone, bovine growth hormone, growth hormone-releasing hormone, an interferon, interleukin-II, insulin, heparin, low molecular weight heparin, calcitonin, erythropoietin, atrial naturetic factor, an antigen, a monoclonal antibody, samatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin,

vasopressin, cromolyn sodium, vancomycin, parathyroid hormone, desferrioxamine (DFO), or any combination thereof.

22. A composition as defined in claim 21, wherein said biologically active agent comprises an interferon, interleukin-II, insulin, heparin, low molecular weight heparin, calcitonin, oxytosin, vasopressin, vancomycin, DFO, parathyroid hormone, and combinations thereof.

23. A dosage unit form as defined in claim 8, comprising a tablet, a capsule, or a liquid.

24. A dosage unit form as defined in claim 23, wherein said dosing vehicle is selected from the group consisting of water, 1,2-propane diol, ethanol, or any combination thereof.

25. A dosage unit form as defined in claim 13, comprising a tablet, a capsule, or a liquid.

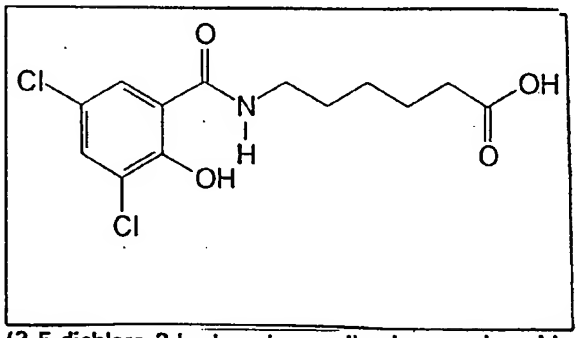
26. A dosage unit form as defined in claim 25, wherein said dosing vehicle is selected from the group consisting of water, 1,2-propane diol, ethanol, or any combination thereof.

27. A dosage unit form as defined in claim 18, comprising a tablet, a capsule, or a liquid.

28. A dosage unit form as defined in claim 27, wherein said dosing vehicle is selected from the group consisting of water, 1,2-propane diol, ethanol, or any combination thereof.

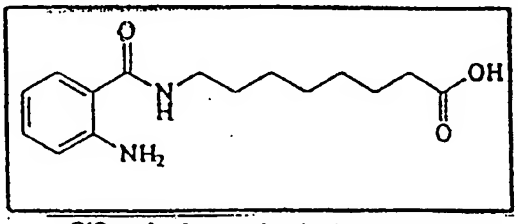
29. A method for administering a biologically-active agent to an animal in need of said agent, said method comprising administering orally to said animal a composition as defined in claim 2.

30. A compound selected from the group consisting of



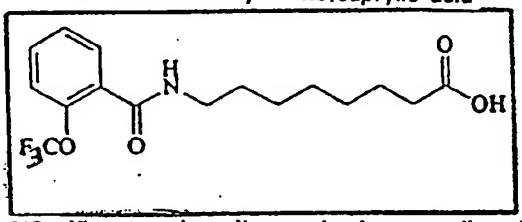
1

6-N-(3,5-dichloro-2-hydroxybenzoyl)aminocaproic acid



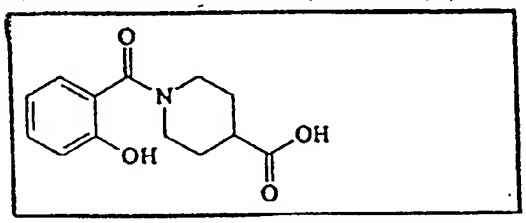
2

8(2-aminobenzoylamino)caprylic acid



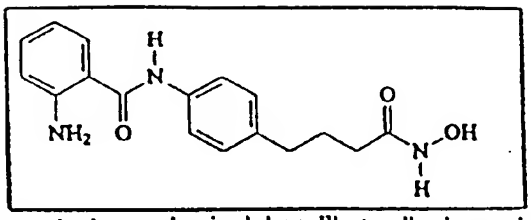
3

8(2-trifluoromethoxy)benzoylamino caprylic acid



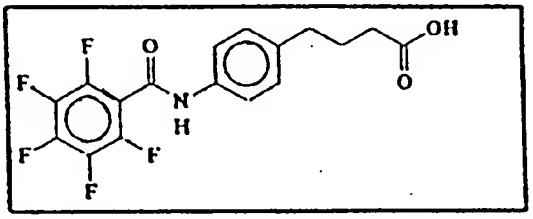
4

N-(2-hydroxybenzoyl)isonipecotic acid



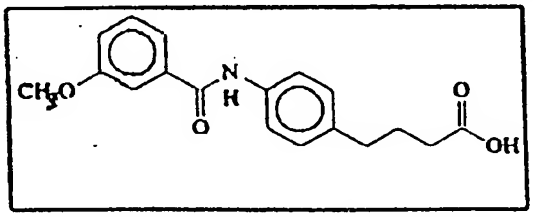
5

4-[4-(2-aminobenzoylamino)phenyl]butyrylhydroxamic acid



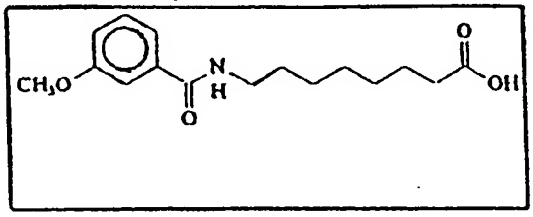
6

4-(4-(pentafluorobenzoyl)aminophenyl)butyric acid



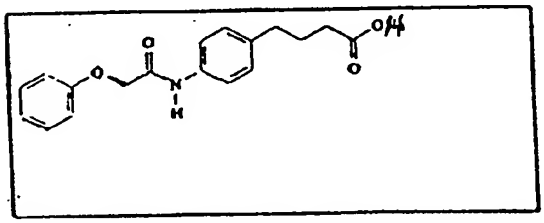
7

4-(4-(3-anisoyl)aminophenyl)butyric acid



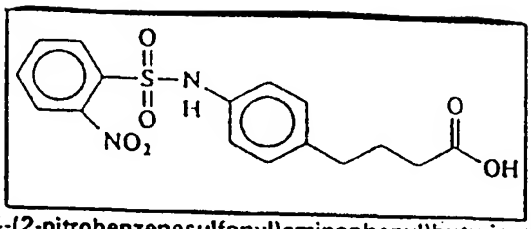
8

8-(3-anisoyl)aminocaprylic acid



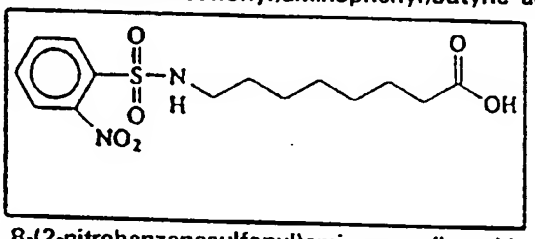
9

4-(4-(phenoxyacetyl)aminophenyl)butyric acid



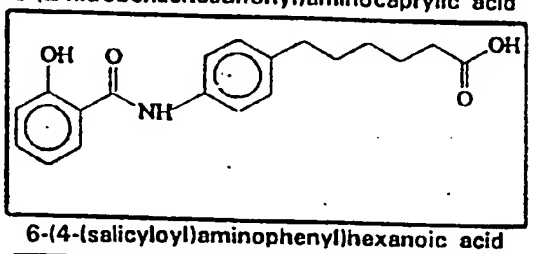
10

4-(4-(2-nitrobenzenesulfonyl)aminophenyl)butyric acid



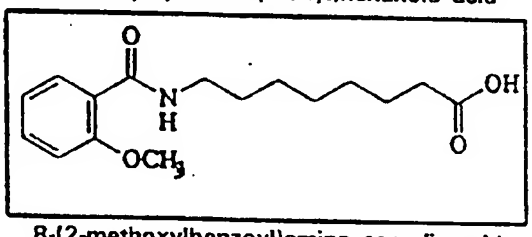
11

8-(2-nitrobenzenesulfonyl)aminocaprylic acid



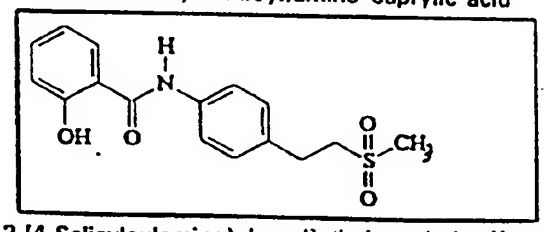
12

6-(4-(salicyloyl)aminophenyl)hexanoic acid



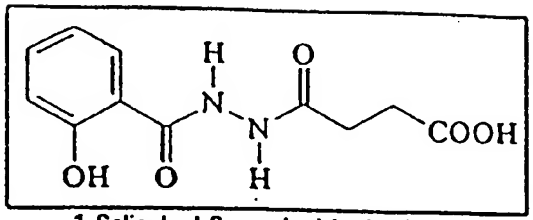
13

8-(2-methoxylbenzoyl)amino caprylic acid



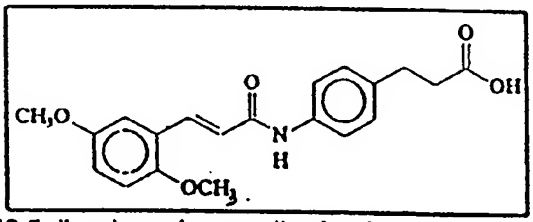
14

2-[4-Salicyloylamino)phenyl]ethyl methyl sulfone



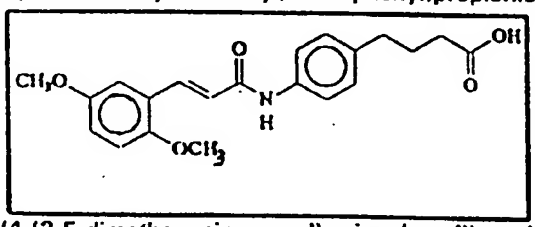
15

1-Salicyloyl-2-succinyl hydrazide



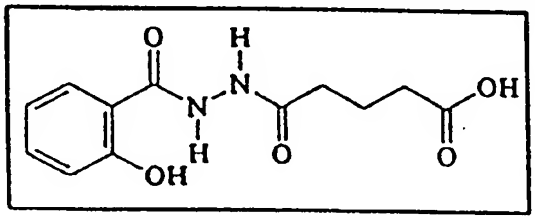
16

3-(4-(2,5-dimethoxycinnamoyl)aminophenyl)propionic acid



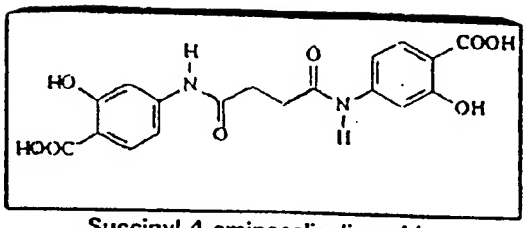
17

4-(4-(2,5-dimethoxycinnamoyl)aminophenyl)butyric acid



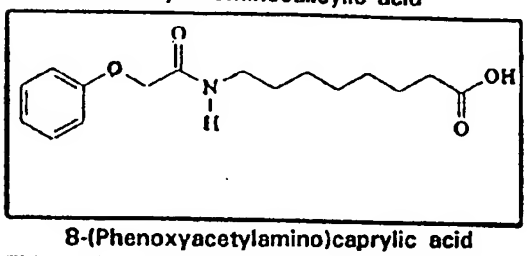
18

1-salicyloyl-2-glutaryl hydrazide



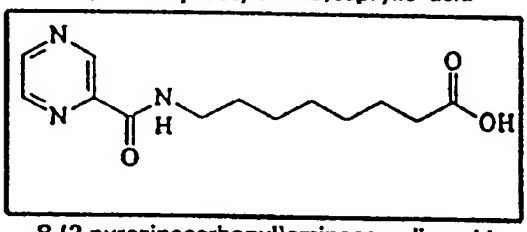
19

Succinyl-4-aminosalicylic acid



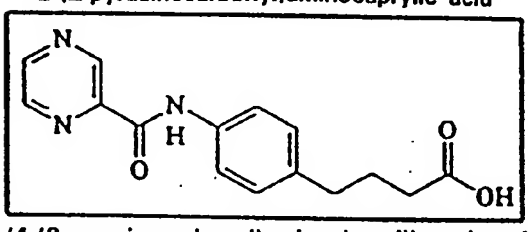
20

8-(Phenoxyacetylamino)caprylic acid



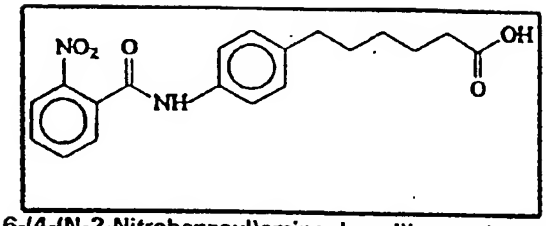
21

8-(2-pyrazinecarbonyl)aminocaprylic acid



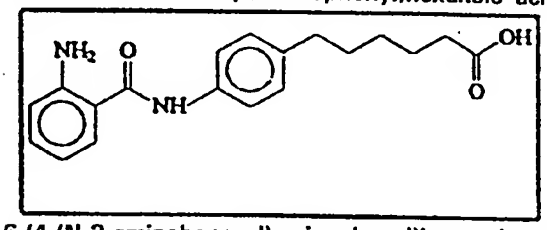
22

4-(4-(2-pyrazinecarbonyl)aminophenyl)butyric acid



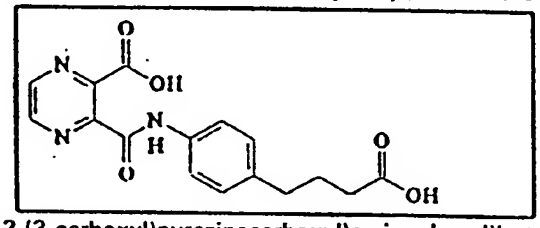
23

6-(4-(N-2-Nitrobenzoyl)aminophenyl)hexanoic acid



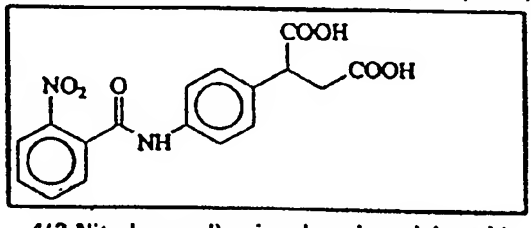
24

6-(4-(N-2-aminobenzoyl)aminophenyl)hexanoic acid



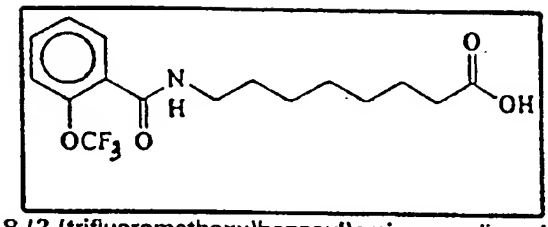
25

4-(4-(2-(3-carboxyl)pyrazinecarboxyl)aminophenyl)butyric acid



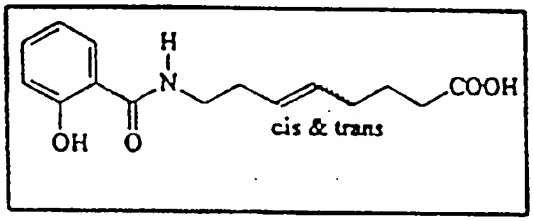
26

4(2-Nitrobenzoyl)aminophenylsuccinic acid

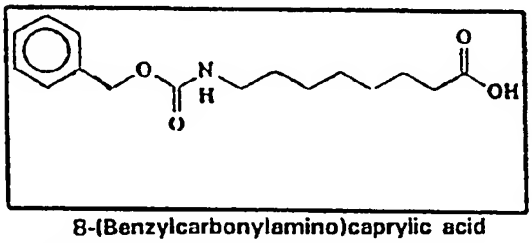


27

8-(2-(trifluoromethoxy)benzoyl)aminocaprylic acid

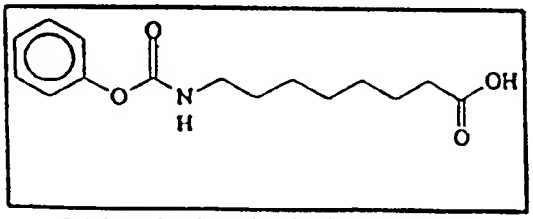


28



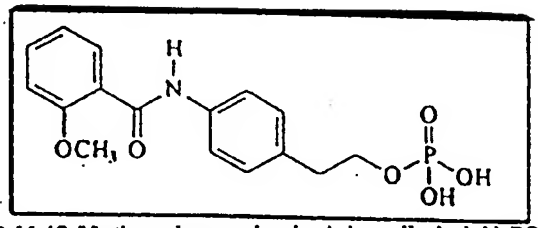
29

8-(Benzylcarbonylamino)caprylic acid



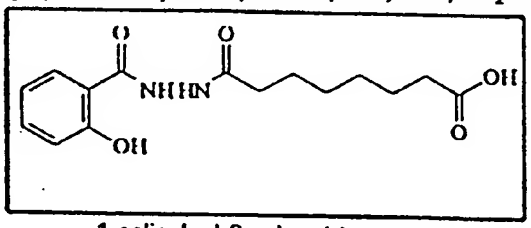
30

8-(phenylcarbonylamino)caprylic acid



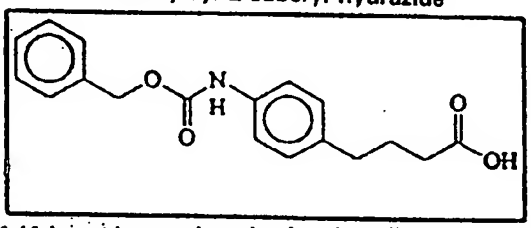
31

2-[4-(2-Methoxybenzoylamino)phenyl]ethyl H_2PO_4



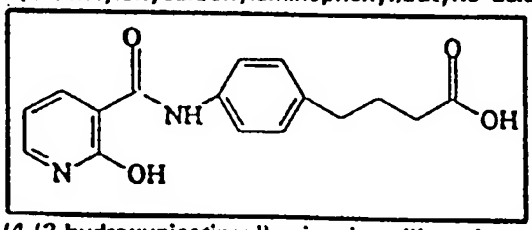
32

1-salicyloyl-2-suberyl hydrazide



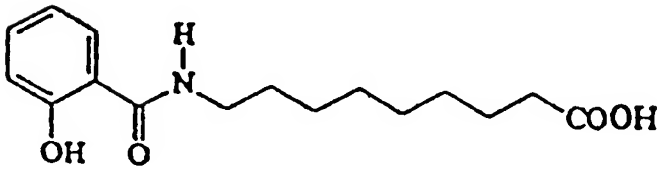
33

4-(4-benzyloxycarbonylaminophenyl)butyric acid

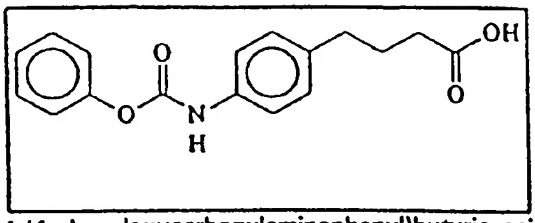


34

4-(4-(2-hydroxynicotinoyl)aminophenyl)butyric acid

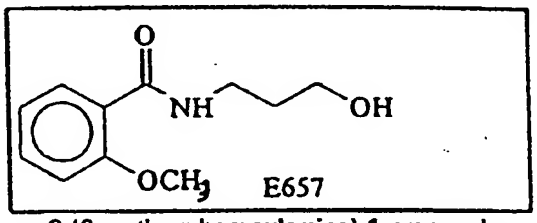


35



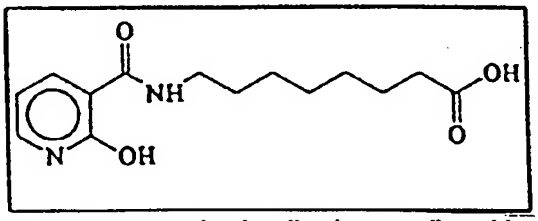
36

4-(4-phenyloxycarbonylaminophenyl)butyric acid



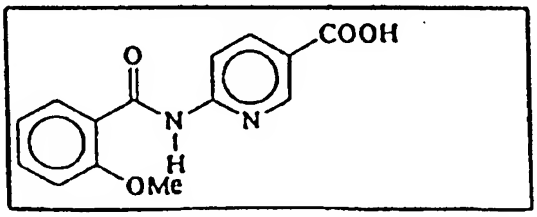
37

3-(2-methoxybenzoylamino)-1-propanol



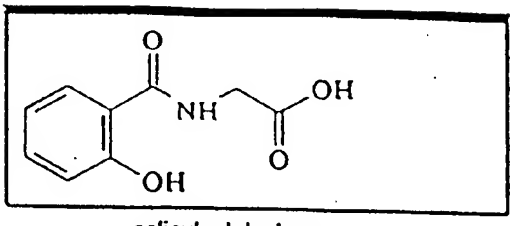
38

8-(2-Hydroxynicotinoyl)aminocaprylic acid



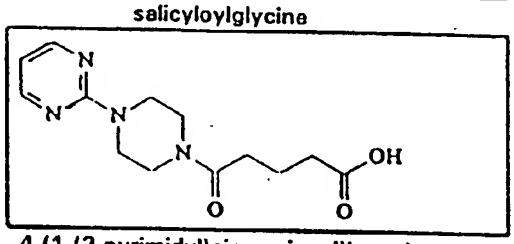
39

6-(2-methoxybenzoyl)amino nicotinic acid



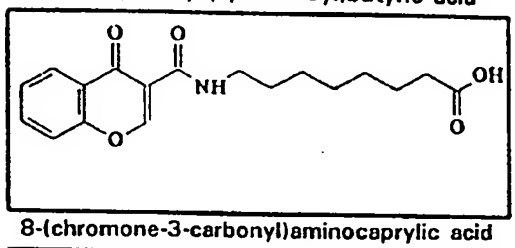
40

salicyloylglycine



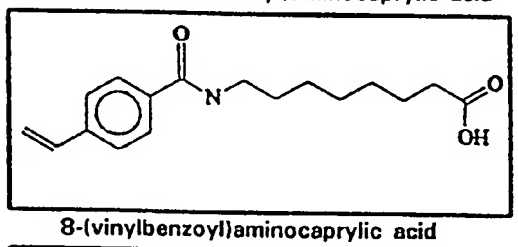
41

4-(1-(2-pyrimidyl)piperazinoyl)butyric acid



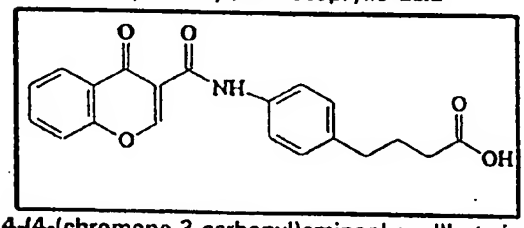
42

8-(chromone-3-carbonyl)aminocaprylic acid



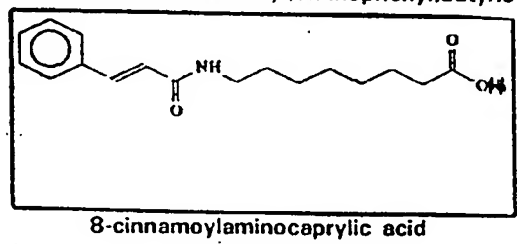
43

8-(vinylbenzoyl)aminocaprylic acid



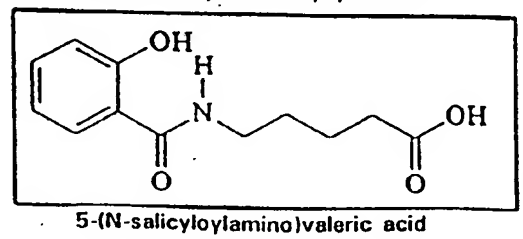
44

4-(4-(chromone-3-carbonyl)aminophenyl)butyric acid



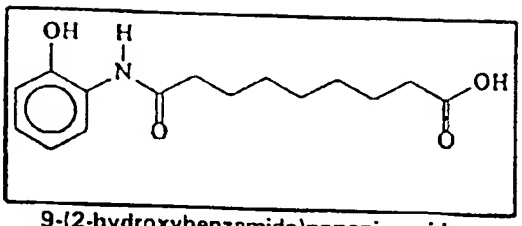
45

8-cinnamoylaminocaprylic acid



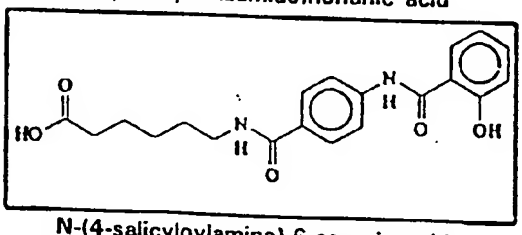
46

5-(N-salicyloylamino)valeric acid



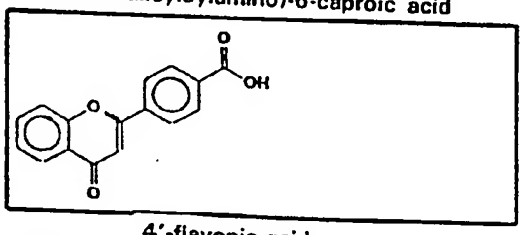
9-(2-hydroxybenzamido)nonanic acid

47



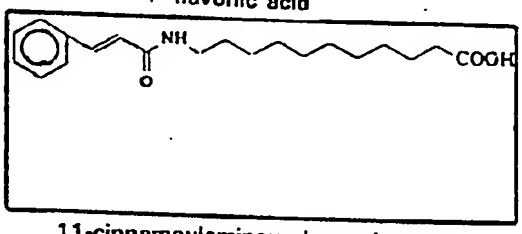
N-(4-salicyloylamino)-6-caproic acid

48



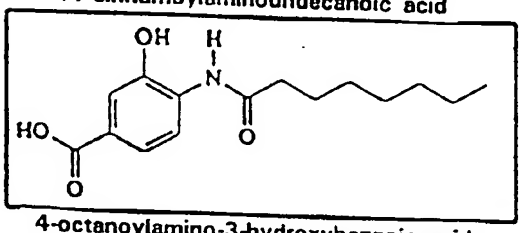
4'-flavonic acid

49



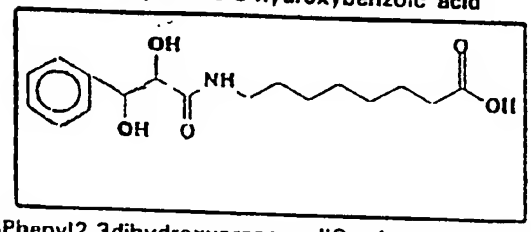
11-cinnamoylaminoundecanoic acid

50



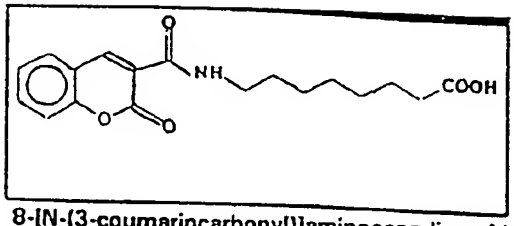
4-octanoylamino-3-hydroxybenzoic acid

51

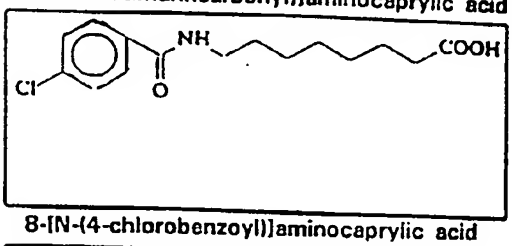


(3Phenyl2,3dihydroxypropanoyl)8aminocaprylic acid

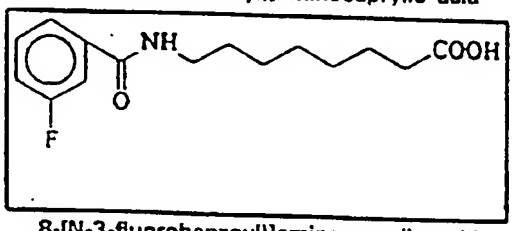
52



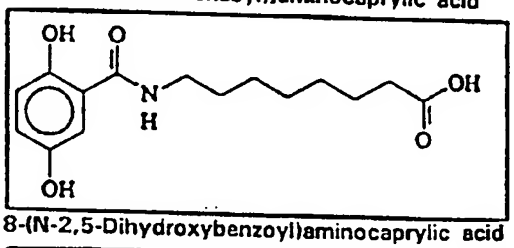
8-[N-(3-coumarincarbonyl)]aminocaprylic acid 53



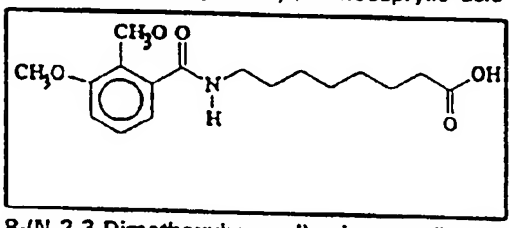
8-[N-(4-chlorobenzoyl)]aminocaprylic acid 54



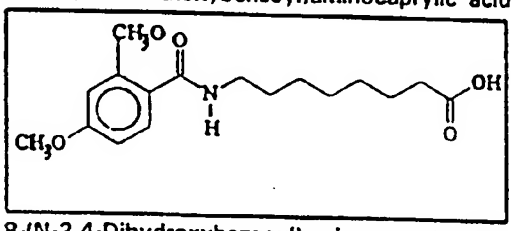
8-[N-3-fluorobenzoyl)]aminocaprylic acid 55



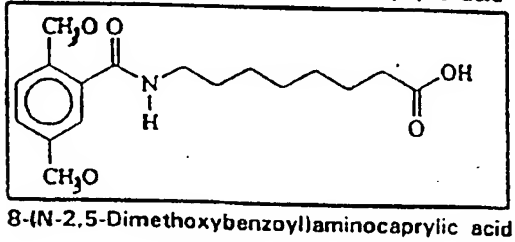
8-(N-2,5-Dihydroxybenzoyl)aminocaprylic acid 56



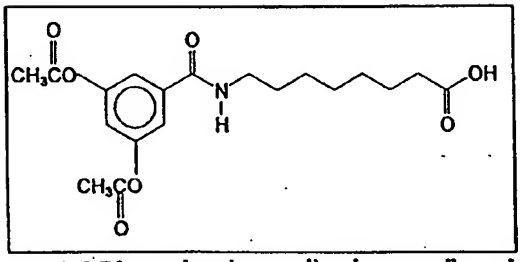
8-(N-2,3-Dimethoxybenzoyl)aminocaprylic acid 57



8-(N-2,4-Dihydroxybenzoyl)aminocaprylic acid 58

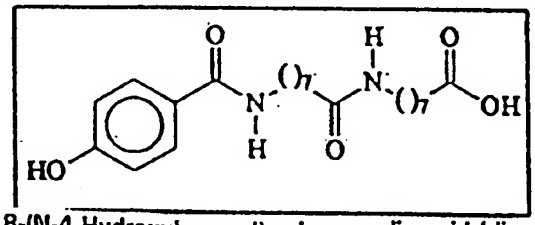


8-(N-2,5-Dimethoxybenzoyl)aminocaprylic acid 59



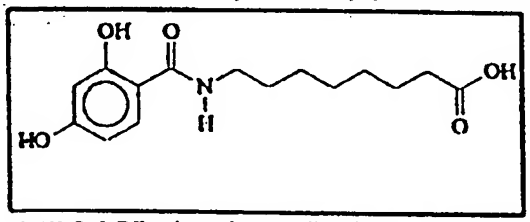
60

8-(N-3,5-Diacetyloxybenzoyl)aminocaprylic acid



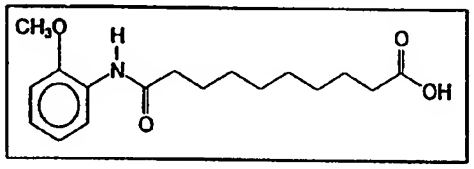
61

8-(N-4-Hydroxybenzoyl)aminocaprylic acid (dimer)



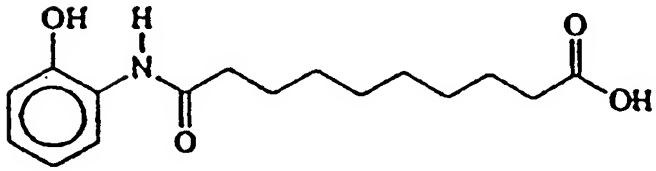
62

8-(N-2,4-Dihydroxybenzoyl)aminocaprylic acid

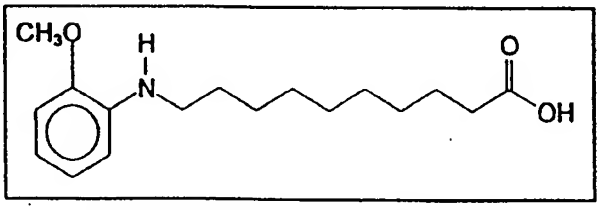


63

10-(N-2-Methoxyanilino)sebalic acid

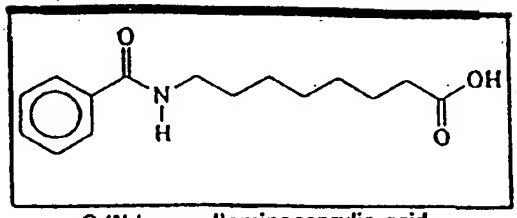


64



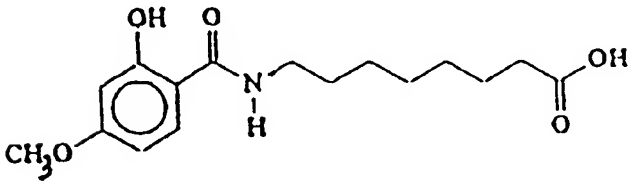
65

2-Methoxybenzenaminodecanoic acid

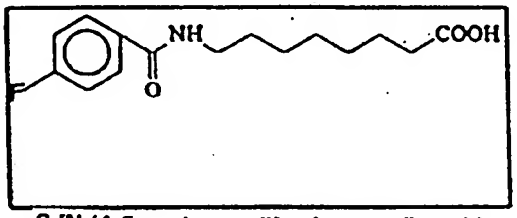


66

8-(N-benzoyl)aminocaprylic acid

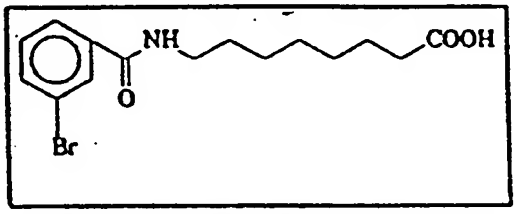


67



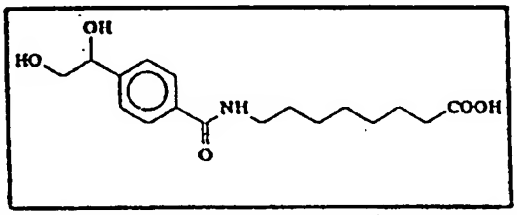
68

8-[N-(4-fluorobenzoyl)]aminocaprylic acid



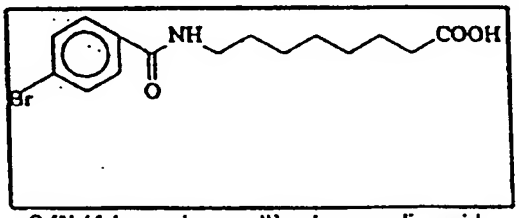
69

8-[N-(3-bromobenzoyl)]aminocaprylic acid



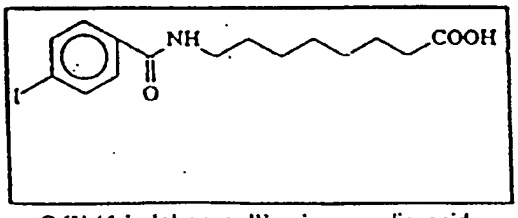
70

8-(4-(1,2-dihydroxyethyl)benzoyl)aminocaprylic acid



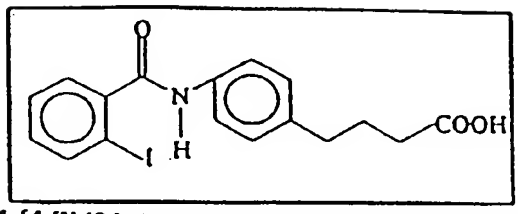
71

8-[N-(4-bromobenzoyl)]aminocaprylic acid



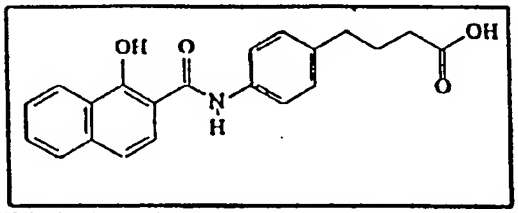
72

8-[N-(4-iodobenzoyl)]aminocaprylic acid



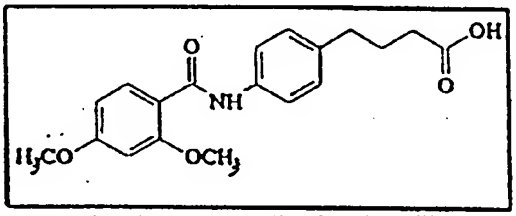
73

4-{4-[N-(2-iodobenzoyl)aminophenyl]}butyric acid



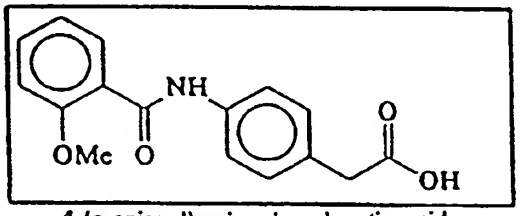
74

4-{4-[N-(1-hydroxy-2-naphthoyl)aminophenyl]}butyric acid



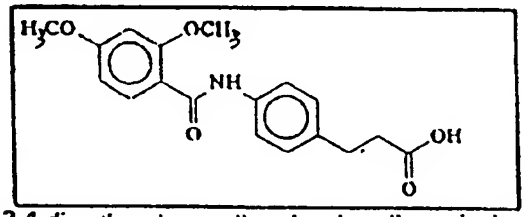
75

4-(4-(2,4-dimethoxylbenzoyl)aminophenyl)butyric acid



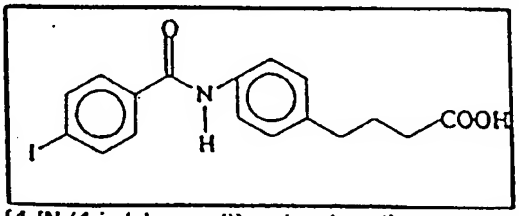
76

4-(o-anisoyl)aminophenylacetic acid



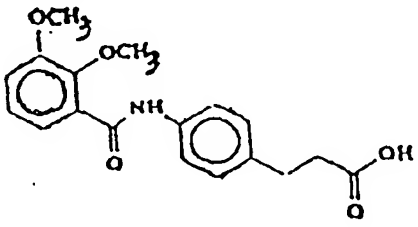
77

3-[4-(2,4-dimethoxybenzoyl) aminophenyl] propionic acid

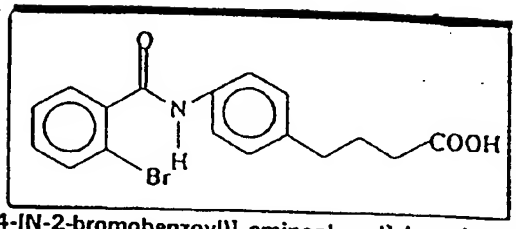


78

4-{4-[N-(4-iodobenzoyl)] aminophenyl} butyric acid

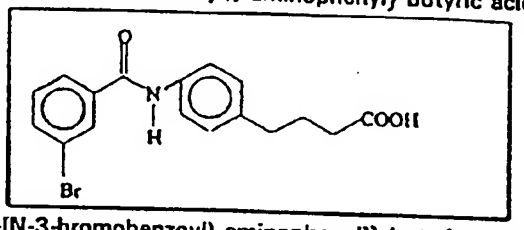


79



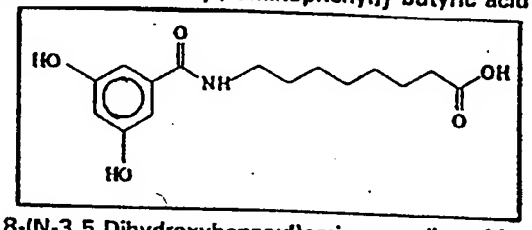
80

4{4-[N-2-bromobenzoyl)] aminophenyl} butyric acid



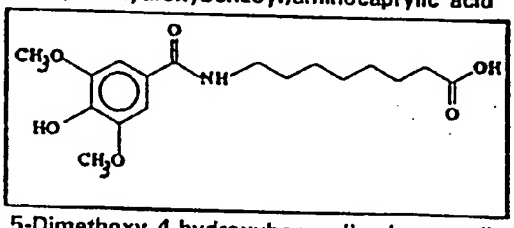
81

4{4-[N-3-bromobenzoyl) aminophenyl]} butyric acid



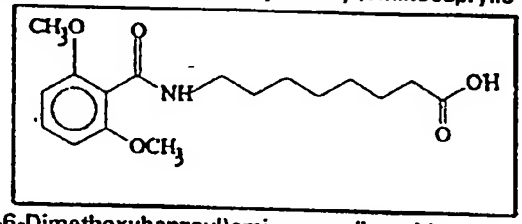
82

8-(N-3,5 Dihydroxybenzoyl)aminocaprylic acid



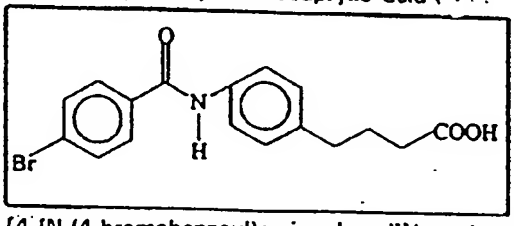
83

8-(N-3,5-Dimethoxy 4-hydroxybenzoyl)aminocaprylic acid



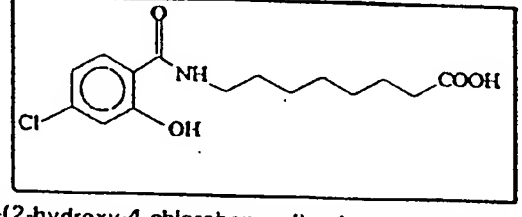
84

8-(N-2-6-Dimethoxybenzoyl)aminocaprylic acid



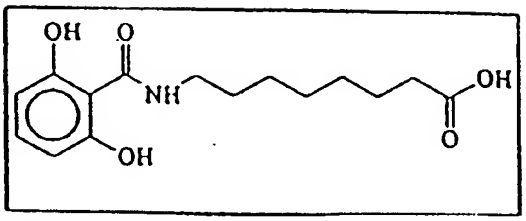
85

4-{4-[N-(4-bromobenzoyl)aminophenyl]}butyric acid



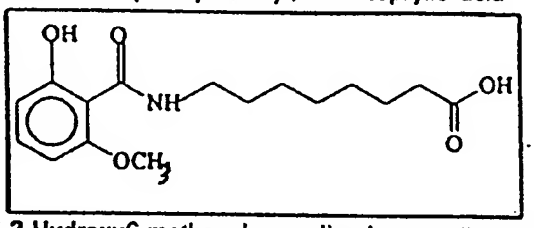
86

8-(2-hydroxy-4-chlorobenzoyl)aminocaprylic acid



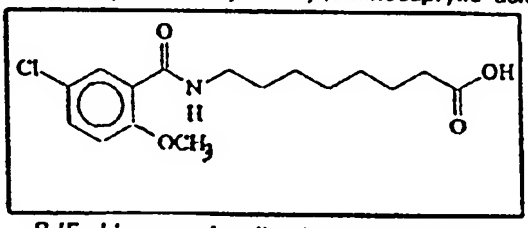
87

8-(N-2,6-Dihydroxybenzoyl)aminocaprylic acid



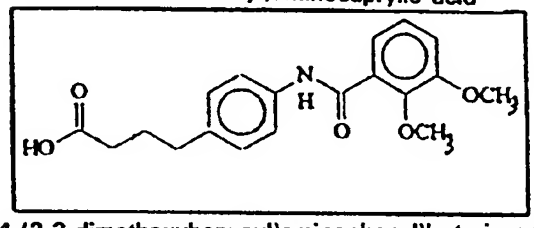
88

8-(N-2-Hydroxy6-methoxybenzoyl)aminocaprylic acid



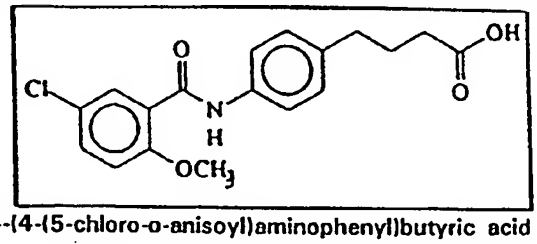
89

8-(5-chloro-o-anisoyl)aminocaprylic acid



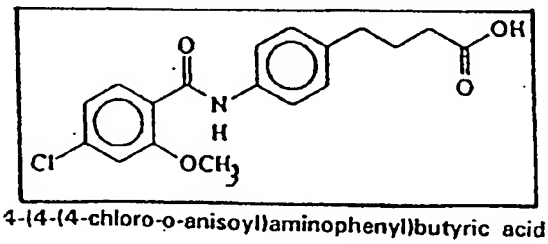
90

4-(4-(2,3-dimethoxybenzoyl)aminophenyl)butyric acid



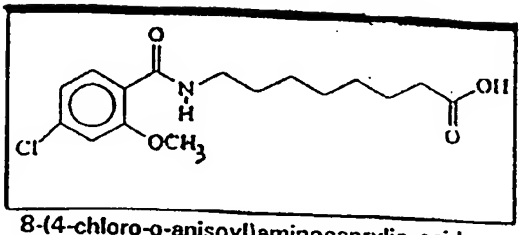
91

4-(4-(5-chloro-o-anisoyl)aminophenyl)butyric acid



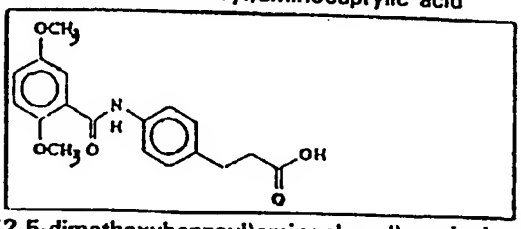
92

4-(4-(4-chloro-o-anisoyl)aminophenyl)butyric acid



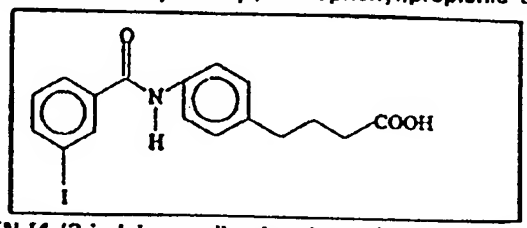
93

8-(4-chloro-o-anisoyl)aminocaprylic acid



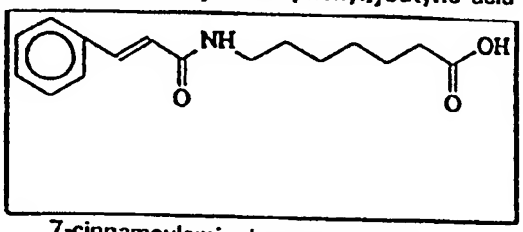
94

3-(4-(2,5-dimethoxybenzoyl)aminophenyl)propionic acid



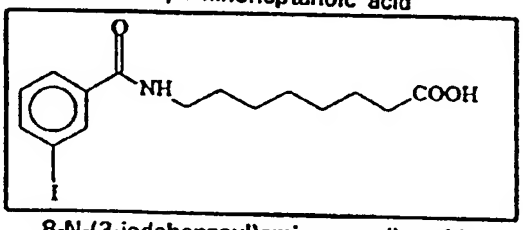
95

4-{N-[4-(3-iodobenzoyl)aminophenyl]}butyric acid



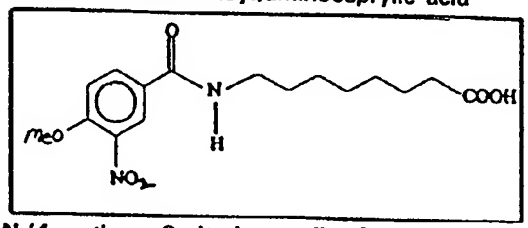
96

7-cinnamoylaminoheptanoic acid



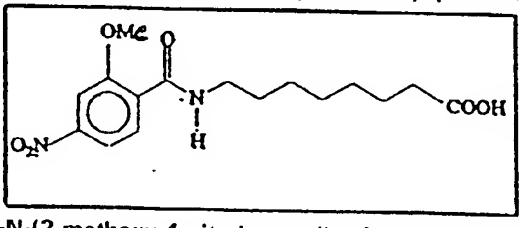
97

8-N-(3-iodobenzoyl)aminocaprylic acid



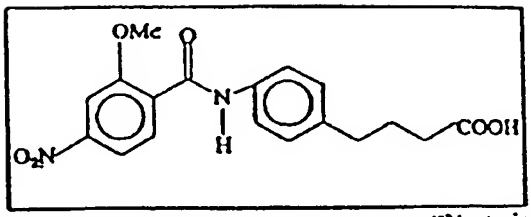
98

8-N-(4-methoxy-3-nitrobenzoyl)aminocaprylic acid



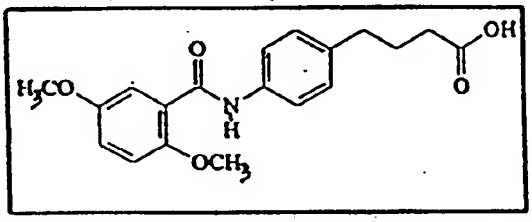
99

8-N-(2-methoxy-4-nitrobenzoyl)aminocaprylic acid



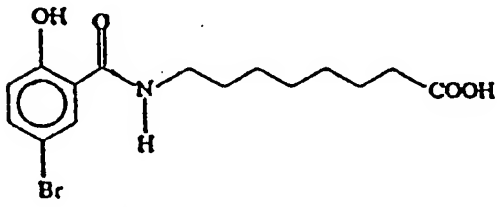
100

4-{N-[4-(2-methoxy-4-nitrobenzoyl)aminophenyl]}butyric acid

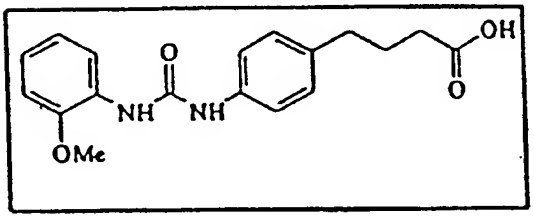


101

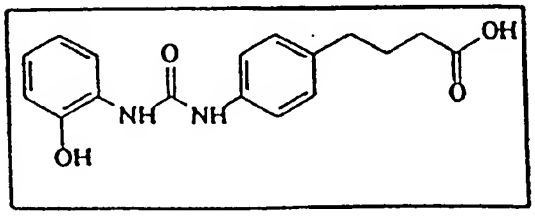
4-(4-(2,5-dimethoxybenzoyl)aminophenyl)butyric acid



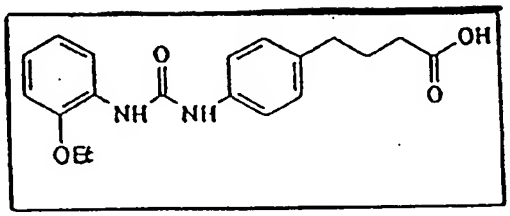
102



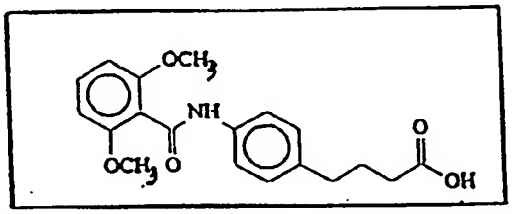
104



105

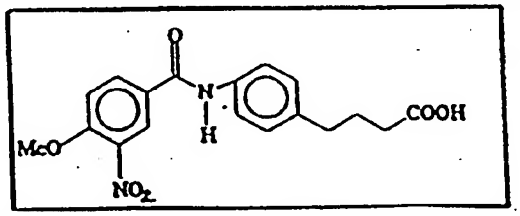


106



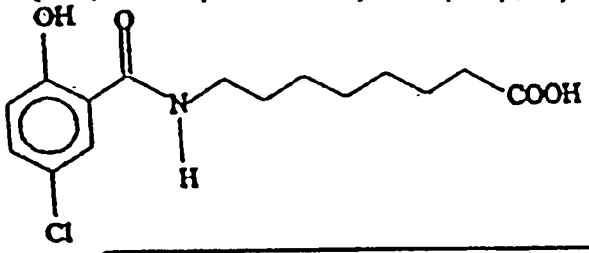
107

4-(4-(2,6-dimethoxybenzoyl)aminophenylbutyric acid

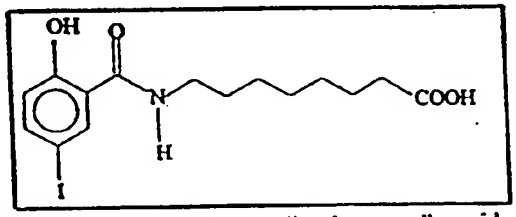


108

4-[4-N-(4-methoxy-3-nitrobenzoyl)aminophenyl]butyric acid

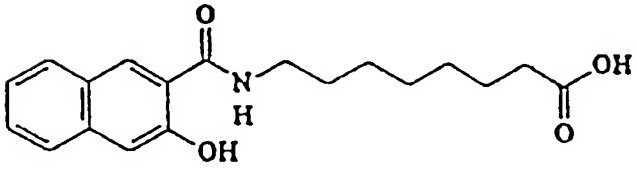


109

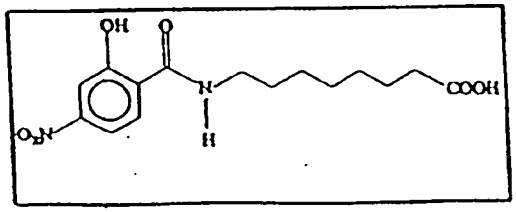


110

8-(N-2-hydroxy-5-iodobenzoyl)aminocaprylic acid

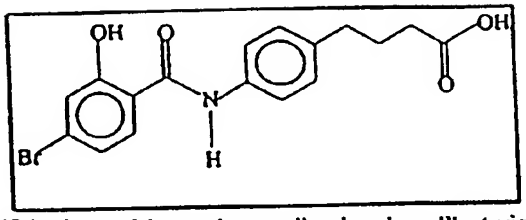


111



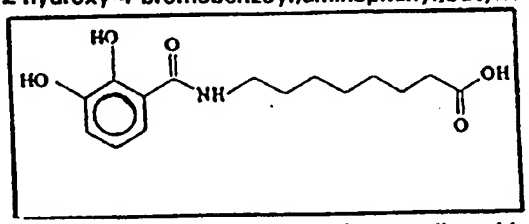
112

8-(N-2-hydroxy-4-nitrobenzoyl)aminocaprylic acid



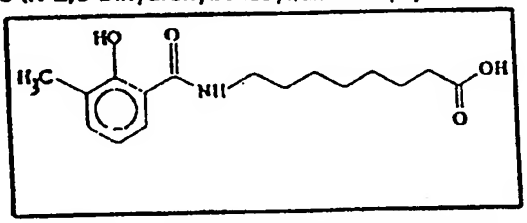
113

4-[-N-(2-hydroxy-4-bromobenzoyl)aminophenyl]butyric acid



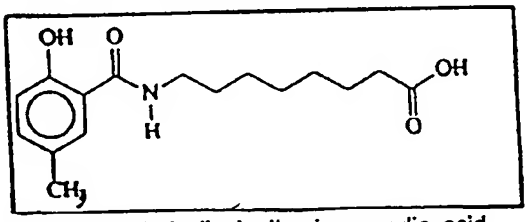
114

8-(N-2,3-Dihydroxybenzoyl)aminocaprylic acid



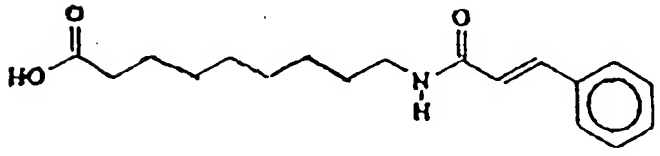
115

8-(N-3-methylsalicyloyl)aminocaprylic acid

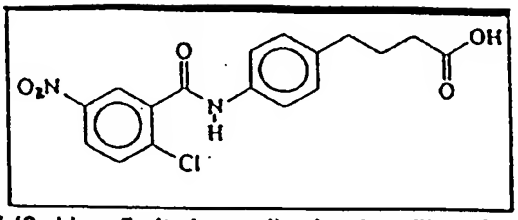


116

8-(N-5-methylsalicyloyl)aminocaprylic acid

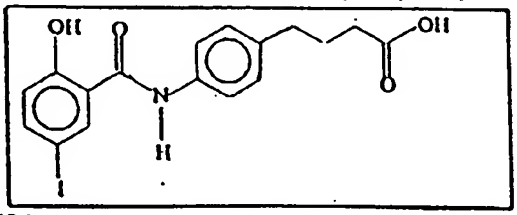


117



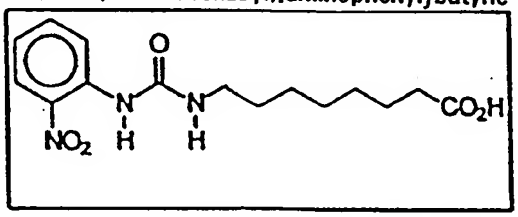
118

4-(4-(2-chloro-5-nitrobenzoyl)aminophenyl)butyric acid



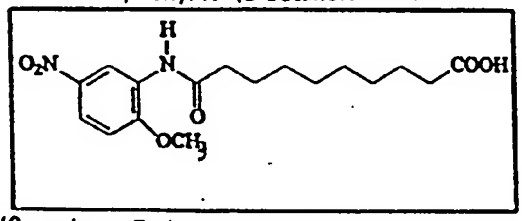
119

4-{-[N-(2-hydroxy-5-iodobenzoyl)]aminophenyl}butyric acid



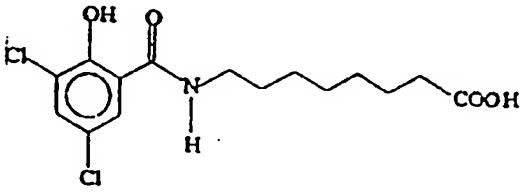
120

N-2-nitrophenyl-N'-(8-octanoic acid) urea

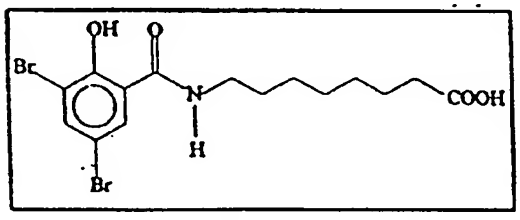


121

N-(2-methoxy-5-nitrophenyl) sebecoyl amide acid

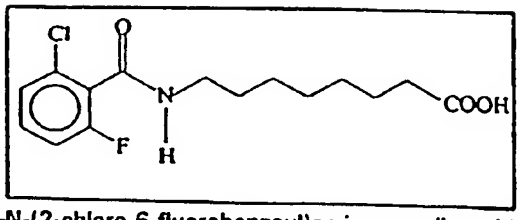


122



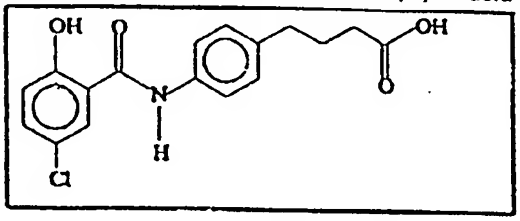
123

8-[N-(2-acetoxy-3,5-dibromobenzoyl)]aminocaprylic acid

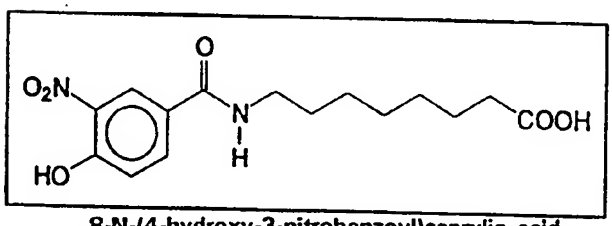


124

8-N-(2-chloro-6-fluorobenzoyl)aminocaprylic acid

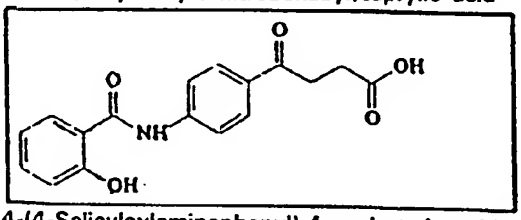


125



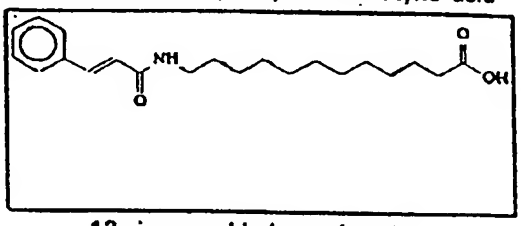
126

8-N-(4-hydroxy-3-nitrobenzoyl)caprylic acid



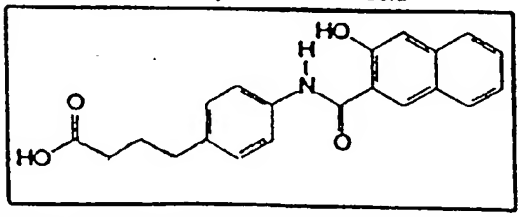
127

4-(4-Salicyloylaminophenyl)-4-oxobutyric acid



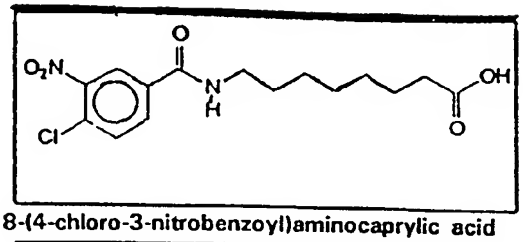
128

12-cinnamoyldodecanoic acid



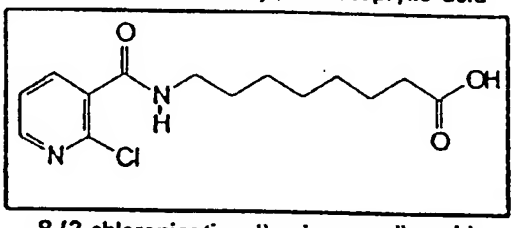
129

4-{4-[N-(3-hydroxy-2-napthoyl)aminophenyl]}butyric acid



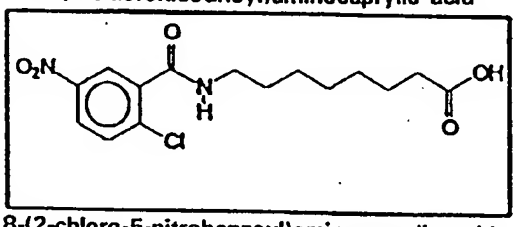
8-(4-chloro-3-nitrobenzoyl)aminocaprylic acid

130



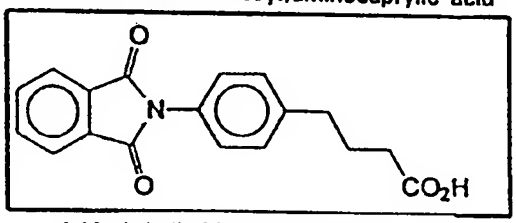
8-(2-chloronicotinoyl)aminocaprylic acid

131



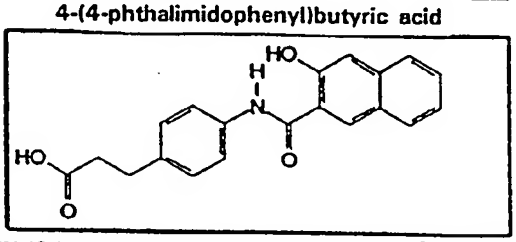
8-(2-chloro-5-nitrobenzoyl)aminocaprylic acid

132



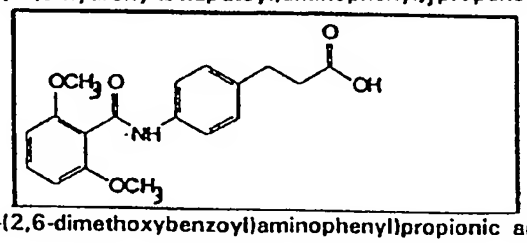
4-(4-phthalimidophenyl)butyric acid

133



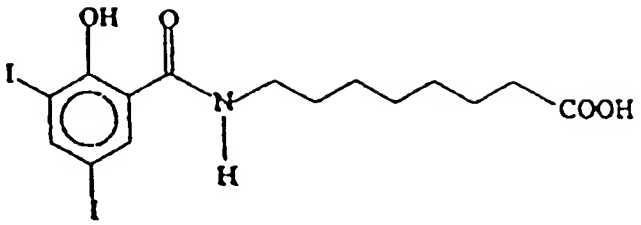
4-{4-[N-(3-hydroxy-2-napthoyl)aminophenyl]}propanoic acid

134

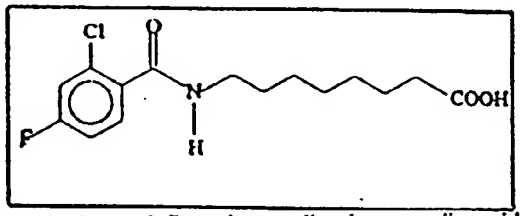


3-(4-(2,6-dimethoxybenzoyl)aminophenyl)propionic acid

135

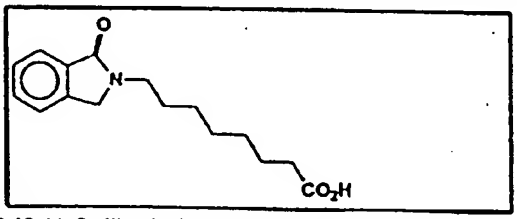


136



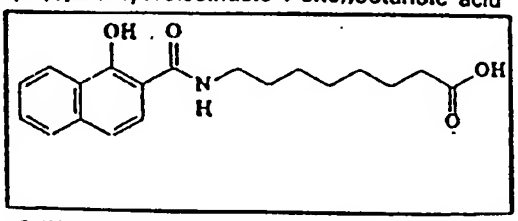
137

8-(N-2-chloro-4-fluorobenzoyl)aminocaprylic acid



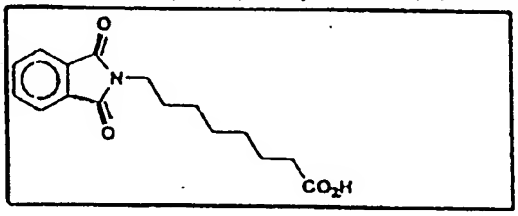
138

8-(2-(1,2-dihydroisoindole-1-one))octanoic acid



139

8-(N-1-hydroxy-2-naphthoyl)aminocaprylic acid

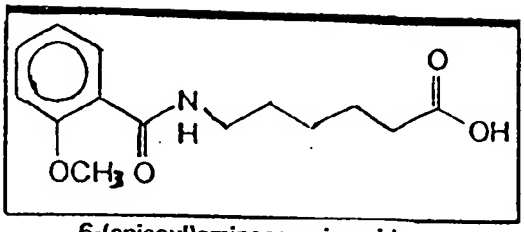


140

8-(phthalimido)caprylic acid

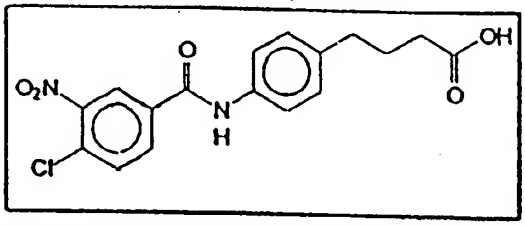
141

142



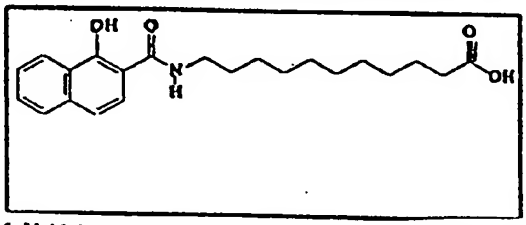
6-(anisoyl)aminocaproic acid

143



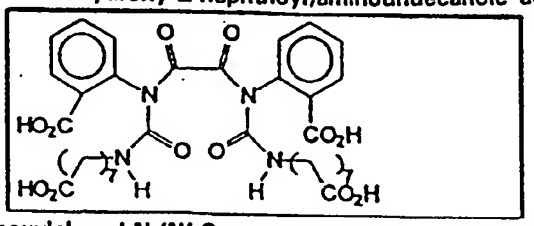
4-(4-(4-chloro-3-nitrobenzoyl)aminophenyl)butyric acid

144



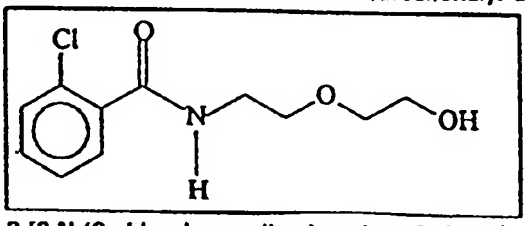
11-N-(1-hydroxy-2-naphthoyl)aminoundecanoic acid

145



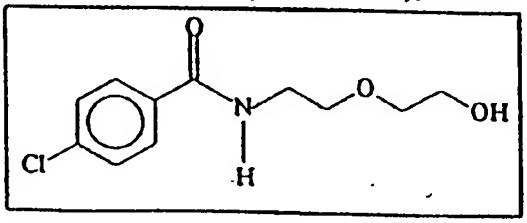
Bis(N-2carboxylphenyl-N-(N'-8-octanoic acid)ureal)oxalyl diamide

146

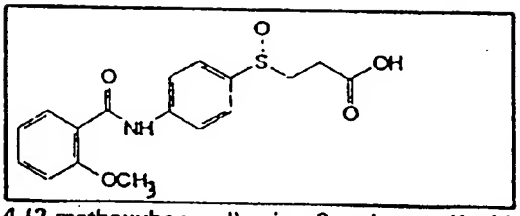


2-[2-N-(2-chlorobenzoyl)aminoethoxy]ethanol

147

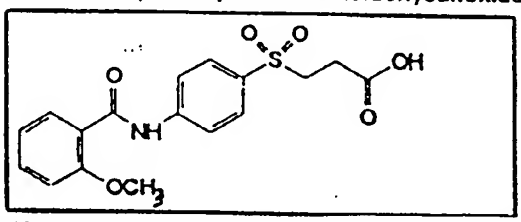


2-[2-N-(4-chlorobenzoyl)aminoethoxy]ethanol



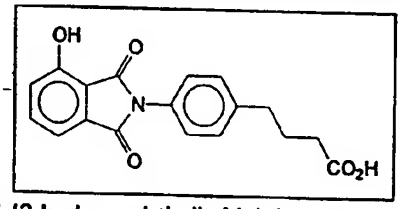
148

4-(2-methoxybenzoyl)amino 3-carboxysulfoxide



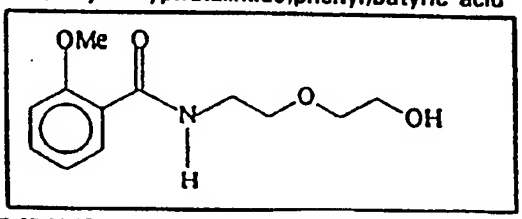
149

4-(2-methoxybenzoyl)amino 3-carboxypropylsulfone



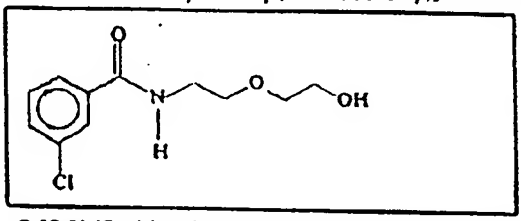
150

4-(4-(3-hydroxyphthalimido)phenyl)butyric acid



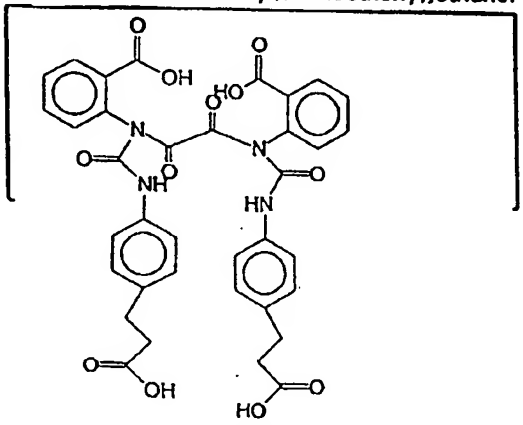
151

2-(2-N-(2-methoxybenzoyl)aminoethoxy))ethanol



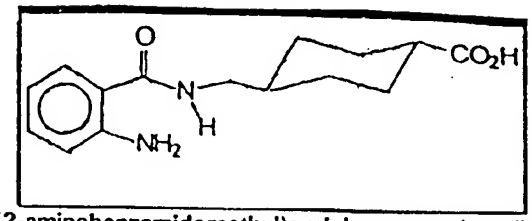
152

2-(2-N-(3-chlorobenzoyl)aminoethoxy))ethanol



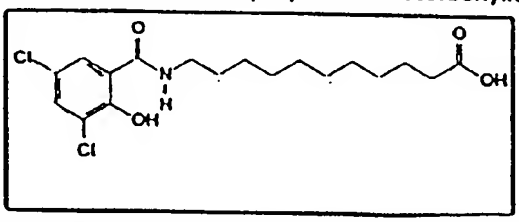
153

Bis(N-2-carboxyphenyl-N-(N'-3(4-aminophenyl)propionic acid)ureal)oxaylyl diamide



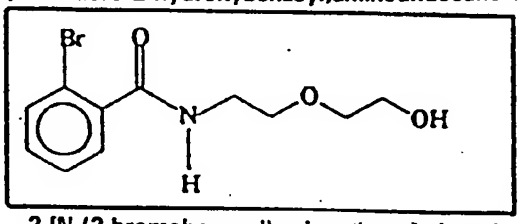
154

trans-4-(2-aminobenzamidomethyl)cyclohexamecarboxylic acid



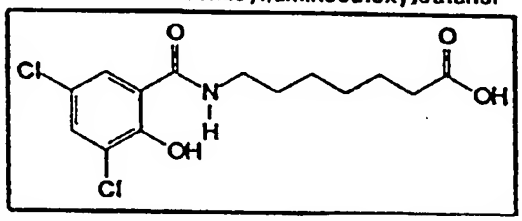
155

11-N-(3,5-dichloro-2-hydroxybenzoyl)aminoundecanoic acid



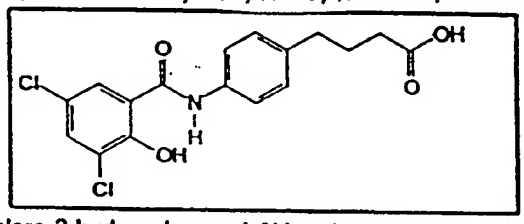
156

2-[N-(2-bromobenzoyl)aminoethoxy]ethanol



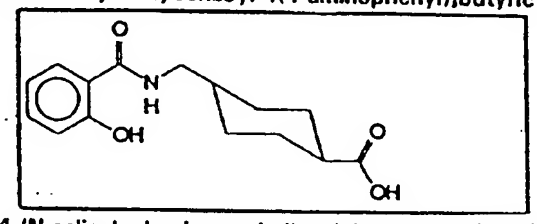
157

7-N-(3,5-dichloro-2-hydroxybenzoyl)aminoheptanoic acid



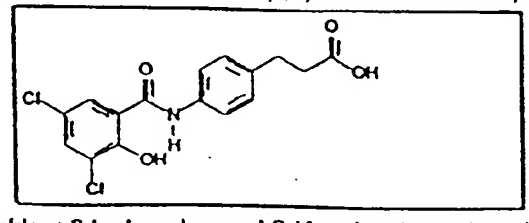
158

N-[3,5-dichloro-2-hydroxybenzoyl-4(4-aminophenyl)]butyric acid



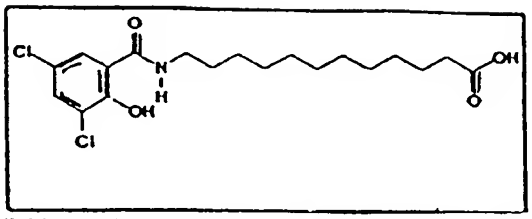
159

trans-4-(N-salicyloylaminomethyl)cyclohexane carboxylic acid



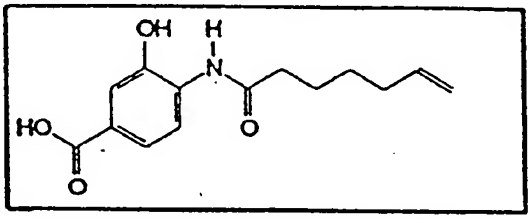
160

N-[3,5-dichloro-2-hydroxybenzoyl-3-(4-aminophenyl)]propionic acid



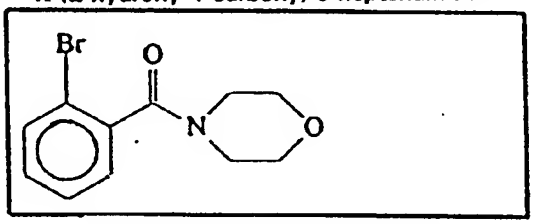
12-N-(3,5-dichloro-2-hydroxybenzoyl)aminododecanoic acid

161



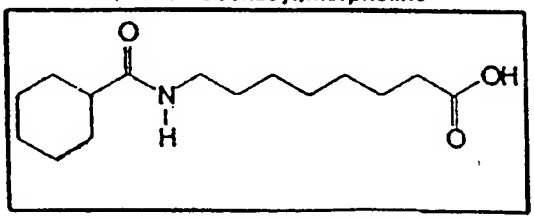
N-(2-hydroxy-4-carboxy)-6-heptenamide

162



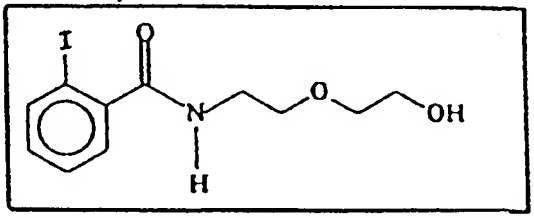
N-(2-bromobenzoyl)morpholine

163



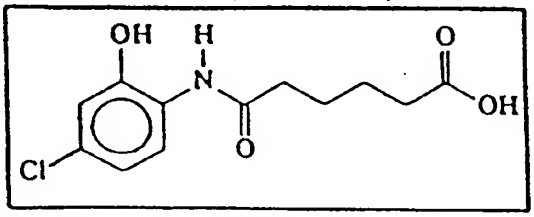
8-N-cyclohexanoylaminocaprylic acid

164



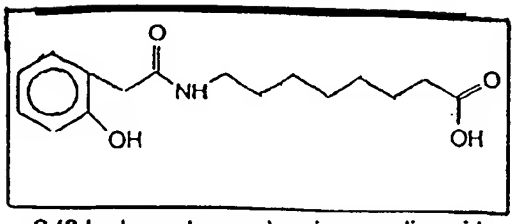
2-[N-(2-iodobenzoyl)aminoethoxy]ethanol

165



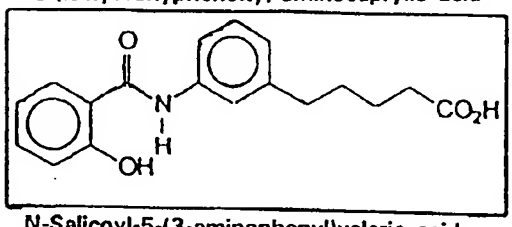
5-(4-chloro-2-hydroxyanilinocarbonyl)valeric acid

166



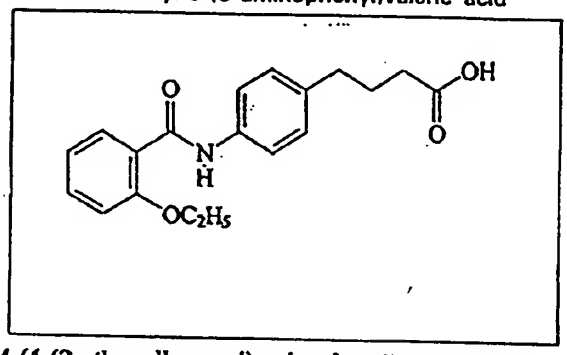
167

8-(2-hydroxyphenoxy)-aminocaprylic acid



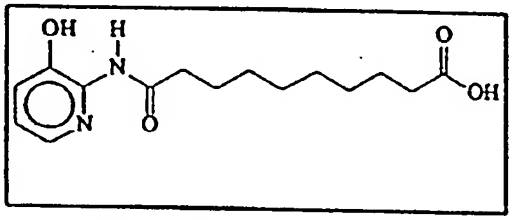
168

N-Salicoyl-5-(3-aminophenyl)valeric acid



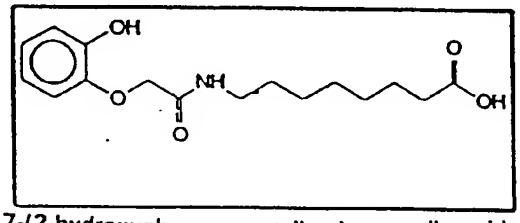
169

4-(4-(2-ethoxylbenzoyl)aminophenyl)butyric acid



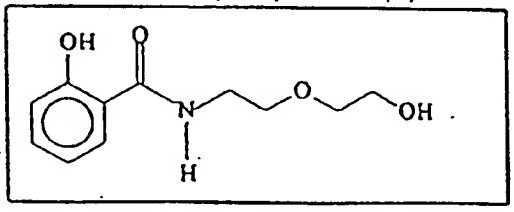
170

9-[2-(3-hydroxy)pyridylaminocarbonyl] nonanic acid



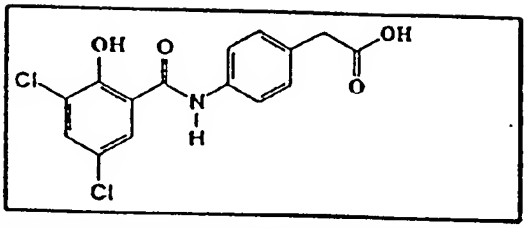
171

7-(2-hydroxyphenoxyacetyl)aminocaprylic acid



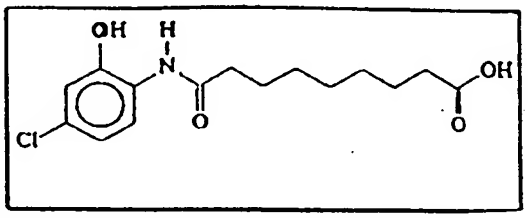
172

2-[N-(2-hydroxybenzoylamino)ethoxy]ethanol



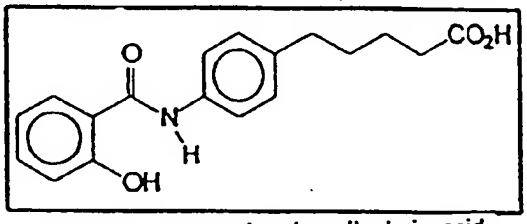
173

4-[N-(3,5-dichloro-2-hydroxybenzoyl)]aminophenylacetic acid



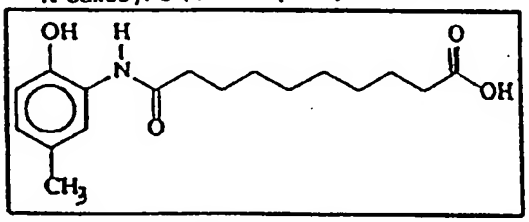
174

8-(2-hydroxy-5-chloroanilinocarbonyl)octanoic acid



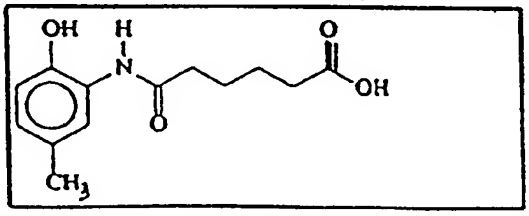
175

N-salicoyl-5-(4-aminophenyl)valeric acid



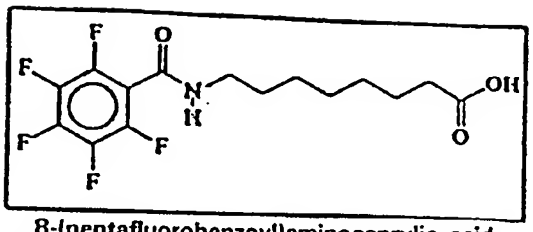
176

9-(2-hydroxy-5-methylanilinocarbonyl)nonanoic acid



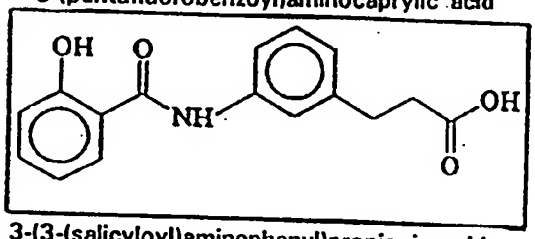
177

5-(2-hydroxy-5-methylanilinocarbonyl)valeric acid



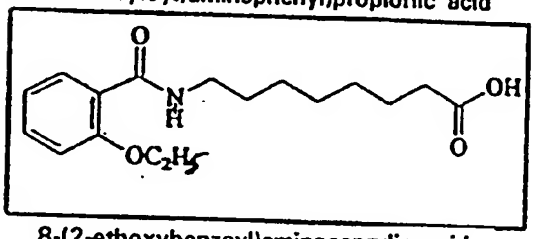
178

8-(pentafluorobenzoyl)aminocaprylic acid



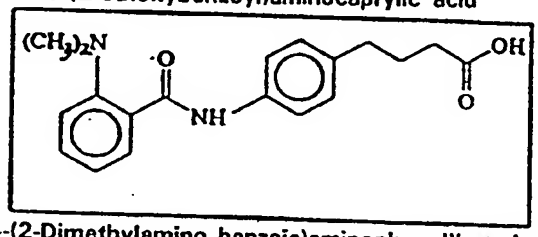
179

3-(3-(salicyloyl)aminophenyl)propionic acid



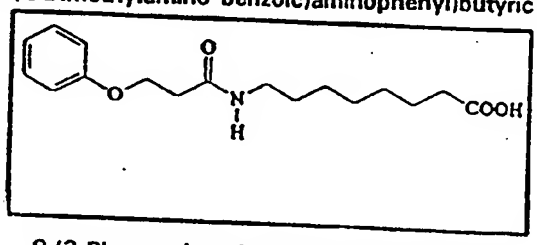
180

8-(2-ethoxybenzoyl)aminocaprylic acid



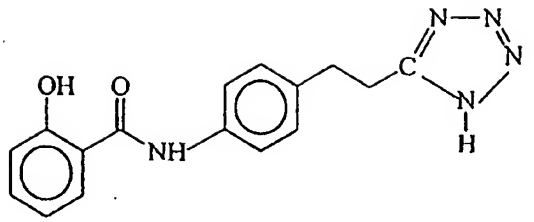
181

4-(4-(2-Dimethylamino benzoic)aminophenyl)butyric acid



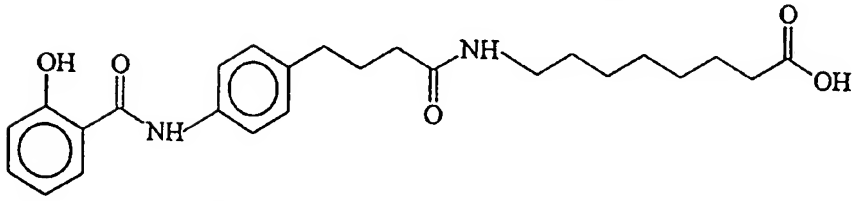
182

8-(3-Phenoxylpropionylamino)caprylic acid



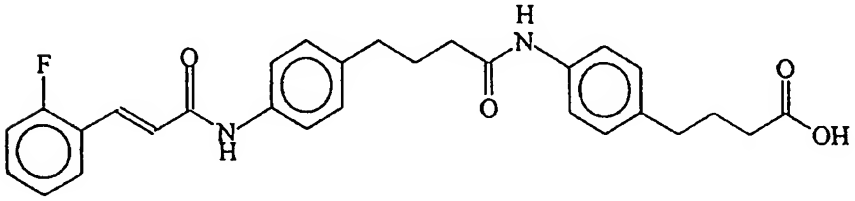
183

4-(Salicyloyl)aminophenylethyltetrazole



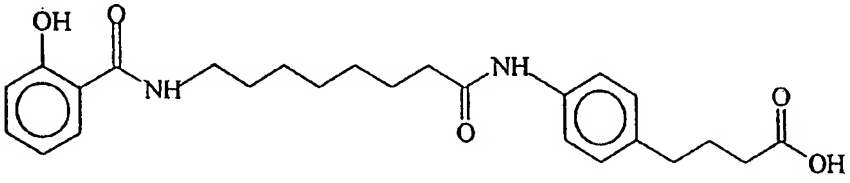
184

8(-(4(N-Saliciloyl-4aminophenyl)butyric)aminocaprylic acid [sic]



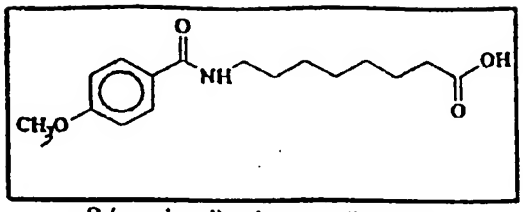
185

4-(4-(N-(2-Fluorocinnamoyl))aminophenyl) butyric



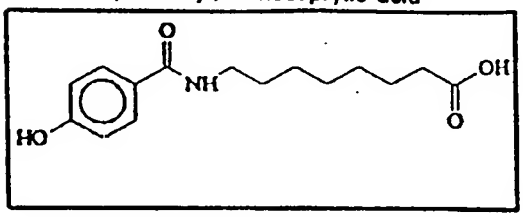
186

4-(4-(N-8(N-Salicyloyl)aminocaprylic)aminophenyl)butyric acid



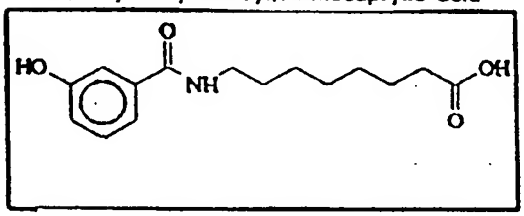
187

8-(p-anisoyl)aminocaprylic acid



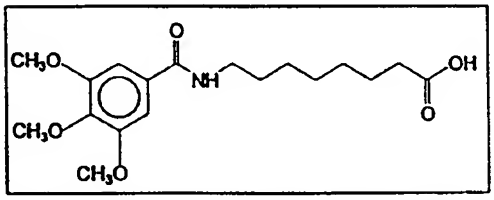
188

8-(4-Hydroxybenzoyl)aminocaprylic acid



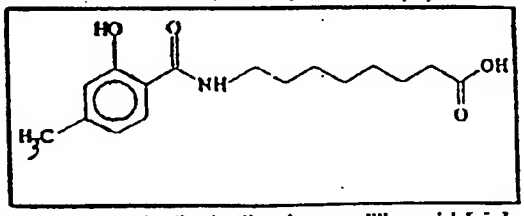
189

8-(3-Hydroxybenzoyl)aminocaprylic acid



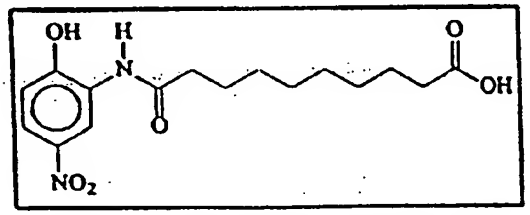
190

8-(3,4,5-Trimethoxybenzoyl)aminocaprylic acid



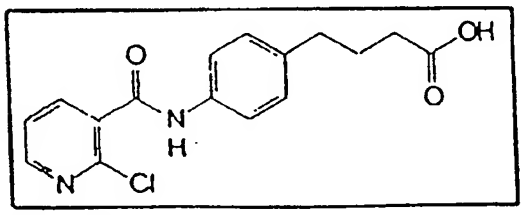
191

8-(N-4-Methylsalicyloyl)aminocaprillic acid [sic]



192

N-10-(2-hydroxy-5-nitroanilino)decanoic acid



193

4-(4-(2-chloronicotinoyl)aminophenyl)butyric acid

37. A method for administering a biologically active agent to an animal in need of said agent, said method comprising administering vaginally to said animal a composition as defined in claim 2.

38. A method for administering a biologically active agent to an animal in need of said agent, said method comprising administering bucally to said animal a composition as defined in claim 2.

39. A method for administering a biologically active agent to an animal in need of said agent, said method comprising administering ophthalmically to said animal a composition as defined in claim 2.

40. A method for passing a biologically active agent across the blood/brain barrier of an animal in need of said agent, said method comprising administering to said animal a composition as defined in claim 2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/02619

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, Chemical Abstracts
search terms: oral, carrier, chemical structures

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,541,155 A (LEONE-BAY ET AL) 30 July 1996 (30/07/96).	1-30, 37-40
X	US 4,238,506 A (STACH, DECEASED ET AL) 09 December 1980 (09/12/80), column 1, lines 11-34, column 6, line 55 - column 7, line 11.	1-3, 8-10, 23, 24, 29, 30, 40
X,P	US 5,705,529 A (MATYUS ET AL) 06 January 1998 (06/01/98), column 1, lines 8-51, column 8, lines 55-57, column 11, lines 4-26.	1-3, 8-10, 23, 24, 29, 30, 40
X	WO 96/30036 A1 (EMISPHERE TECHNOLOGIES, INC.) 03 October 1996 (03/10/96), see entire document.	1-30, 37-40

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 01 APRIL 1998	Date of mailing of the international search report 29 MAY 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JEFFREY E. RUSSEL Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/02619

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,757,066 A (SHIOKARI ET AL) 12 July 1988 (12/07/88), column 11, lines 61-68, column 12, lines 38-56, column 14, lines 19-26, column 35, lines 12-25.	1, 2, 8, 9, 23, 24, 30, 40
A,P	US 5,643,957 A (LEONE-BAY ET AL) 01 July 1997 (01/07/97).	1-30, 37-40
A,P	US 5,650,386 A (LEONE-BAY ET AL) 22 July 1997 (22/07/97).	1-30, 37-40

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/02619

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 38/00, 47/12; C07C 229/00, 233/00, 317/14; C07D 209/02, 239/02, 241/02, 257/04, 311/04

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

424/85.2, 85.4, 141.1, 184.1; 514/2, 3, 11, 12, 21, 56, 773, 784, 788; 544/242, 336; 548/250, 452; 549/396; 562/11, 405, 553; 564/155

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

424/85.2, 85.4, 141.1, 184.1; 514/2, 3, 11, 12, 21, 56, 773, 784, 788; 544/242, 336; 548/250, 452; 549/396; 562/11, 405, 553; 564/155

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 487/04, A61K 31/55 // (C07D 487/04, 243:00, 209:00) (C07D 487/04, 243:00, 231:00)

A1

(11) International Publication Number: WO 97/49707

(43) International Publication Date: 31 December 1997 (31.12.97)

(21) International Application Number: PCT/US97/10736

(22) International Filing Date: 20 June 1997 (20.06.97)

(30) Priority Data:
08/672,150 27 June 1996 (27.06.96) US

(71) Applicant: AMERICAN CYANAMID COMPANY [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US).

(72) Inventors: ALBRIGHT, Jay, Donald; 5 Clifford Court, Nanuet, NY 10954 (US). VENKATESAN, Aranapakam, Mudumbai; Apartment 9K, 97-07 63rd Road, Rego Park, NY 11374 (US). DUSZA, John, Paul; 24 Convent Road, Nanuet, NY 10954 (US). SUM, Fuk-Wah; 16 Chamberlain Court, Pomona, NY 10970 (US).

(74) Agents: ALICE, Ronald, W.; American Home Products Corporation, Five Giralda Farms, Madison, NJ 07940-0874 (US) et al.

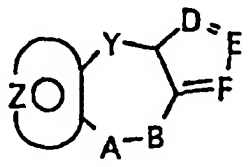
(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: TRICYCLIC BENZAZEPINE VASOPRESSIN ANTAGONISTS

(57) Abstract

Tricyclic compound of general Formula (I), as defined herein which exhibit antagonist activity at V_1 and/or V_2 receptors and exhibit *in vivo* vasopressin antagonist activity, methods for using such compounds in treating diseases characterized by excess renal reabsorption of water, and process for preparing such compounds.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

Title: TRICYCLIC BENZAZEPINE VASOPRESSIN ANTAGONISTS

This case is a continuation-in-part of Serial No. 08/373,132, filed January 17, 1995.

1. Field of the Invention

This invention relates to new tricyclic non-peptide vasopressin antagonists which are useful in treating conditions where decreased vasopressin levels are desired, such as in congestive heart failure, in disease conditions with excess renal water reabsorption and in conditions with increased vascular resistance and coronary vasoconstriction.

2. Background of the Invention

Vasopressin is released from the posterior pituitary either in response to increased plasma osmolarity detected by brain osmoreceptors or decreased blood volume and blood pressure sensed by low-pressure volume receptors and arterial baroreceptors. The hormone exerts its action through two well defined receptor subtypes: vascular V_1 and renal epithelial V_2 receptors. Vasopressin-induced antidiuresis, mediated by renal epithelial V_2 receptors, helps to maintain normal plasma osmolarity, blood volume and blood pressure.

Vasopressin is involved in some cases of congestive heart failure where peripheral resistance is

increased. V_1 antagonists may decrease systemic vascular resistance, increase cardiac output and prevent vasopressin induced coronary vasoconstriction. Thus, in conditions with vasopressin induce increases in total peripheral resistance and altered local blood flow, V_1-antagonists may be therapeutic agents. V_1 antagonists may decrease blood pressure, induced hypotensive effects and thus be therapeutically useful in treatment of some types of hypertension.

The blockage of V_2 receptors is useful in treating diseases characterized by excess renal reabsorption of free water. Antidiuresis is regulated by the hypothalamic release of vasopressin (antidiuretic hormone) which binds to specific receptors on renal collecting tubule cells. This binding stimulates adenylyl cyclase and promotes the cAMP-mediated incorporation of water pores into the luminal surface of these cells. V_2 antagonists may correct the fluid retention in congestive heart failure, liver cirrhosis, nephritic syndrome, central nervous system injuries, lung disease and hyponatremia.

Elevated vasopressin levels occur in congestive heart failure which is more common in older patients with chronic heart failure. In patients with hyponatremic congestive heart failure and elevated vasopressin levels, a V_2 antagonist may be beneficial in promoting free water excretion by antagonizing the action of antidiuretic hormone, On the basis of biochemical and pharmacological effects of the hormone, antagonists of vasopressin are expected to be therapeutically useful in the treatment and/or prevention of hypertension, cardiac insufficiency, coronary vasospasm, cardiac ischemia, renal vasospasm, liver cirrhosis, congestive heart failure, nephritic syndrome, brain edema, cerebral ischemia, cerebral

hemorrhage-stroke, thrombosis-bleeding and abnormal states of water retention.

The following prior art references describe peptide vasopressin antagonists: M. Manning et al., J. Med. Chem., 35, 382(1992); M. Manning et al., J. Med. Chem., 35, 3895(1992); H. Gavras and B. Lammek, U.S. Patent 5,070,187 (1991); M. Manning and W.H. Sawyer, U.S. Patent 5,055,448(1991) F.E. Ali, U.S. Patent 4,766,108(1988); R.R. Ruffolo et al., Drug News and Perspective, 4(4), 217, (May)(1991). P.D. Williams et al., have reported on potent hexapeptide oxytocin antagonists [J. Med. Chem., 35, 3905(1992)] which also exhibit weak vasopressin antagonist activity in binding to V_1 and V_2 receptors. Peptide vasopressin antagonists suffer from a lack of oral activity and many of these peptides are not selective antagonists since they also exhibit partial agonist activity.

Non-peptide vasopressin antagonists have recently been disclosed, Y. Yamamura et al., Science, 252, 579(1991); Y. Yamamura et al., Br. J. Pharmacol, 105, 787(1992); Ogawa et al., (Otsuka Pharm Co., LTD.) EP 0514667-A1; EPO 382185-A2; WO9105549 and U.S.5,258,510; WO 9404525 Yamanouchi Pharm.Co.,Ltd., WO 9420473; WO 9412476; WO 9414796; Fujisawa Co. Ltd., EP 620216-A1 Ogawa et al, (Otsuka Pharm. Co.) EP 470514A disclose carbostyril derivatives and pharmaceutical compositions containing the same. Non-peptide oxytocin and vasopressin antagonist have been disclosed by Merck and Co.; M.G. Bock and P.D. Williams, EP 0533242A; M.G. Bock et al., EP 0533244A; J.M. Erb, D.F. Verber, P.D. Williams, EP 0533240A; K. Gilbert et al., EP 0533243A.

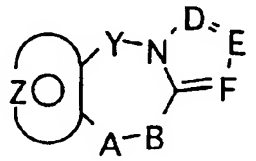
Premature birth can cause infant health problems and mortality and a key mediator in the mechanism of labor is the peptide hormone oxytocin. On the basis of the pharmacological action of oxytocin, antagonists of this hormone are useful in the prevention

of preterm labor, B.E. Evans et al., J. Med. Chem. 35, 3919(1992), J. Med. Chem., 36, 3993(1993) and references therein. The compounds of this invention are antagonists of the peptide hormone oxytocin and are useful in the control of premature birth.

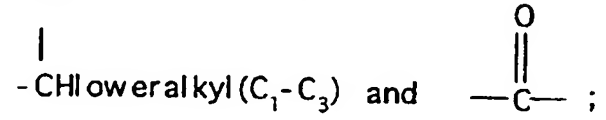
The present invention relates to novel tricyclic derivatives which exhibit antagonist activity at V_1 and/or V_2 receptors and exhibit in vivo vasopressin antagonist activity. The compounds also exhibit antagonist activity at oxytocin receptors.

SUMMARY OF THE INVENTION

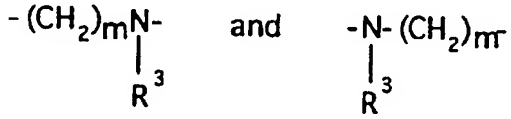
This invention relates to new compounds selected from those of the general formula I:



wherein Y is a moiety selected from; $-(CH_2)_n-$ wherein n is an integer from 0 to 2,



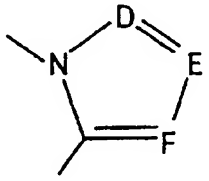
A-B is a moiety selected from



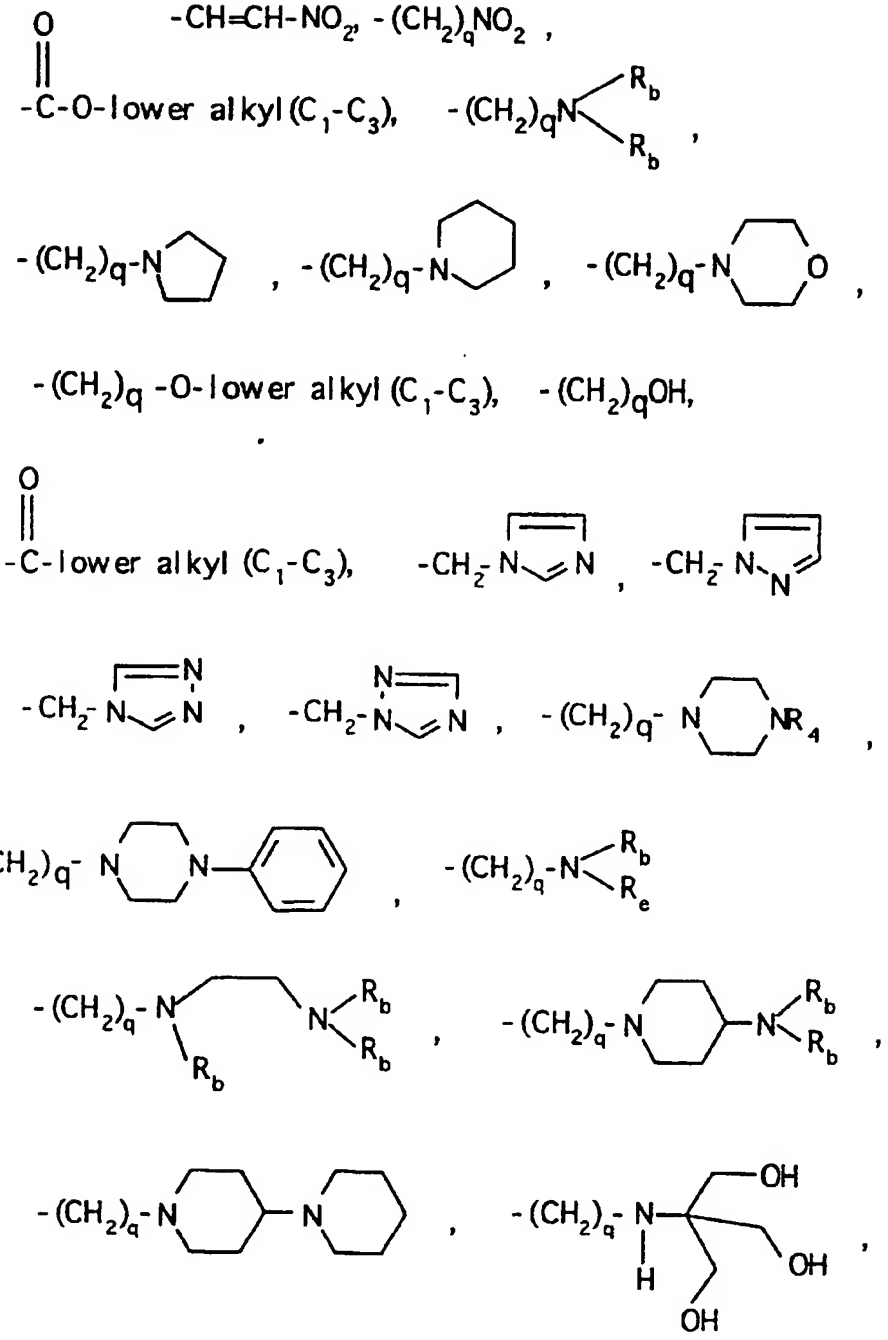
wherein m is an integer from 1 to 2 provided that when Y is $-(CH_2)_n-$ and n is 2, m may also be zero and when n is zero, m may also be three, provided also that when Y is $-(CH_2)_n-$ and n is 2, m may not be two;
and the moiety:

represents: (1) phenyl or substituted phenyl optionally substituted by one or two substituents selected from (C_1-C_3)lower alkyl, halogen, amino, (C_1-C_3)lower alkoxy or (C_1-C_3)lower alkylamino; (2) a 5-membered aromatic (unsaturated) heterocyclic ring having one heteroatom selected from O, N or S; (3) a 6-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom; (4) a 5 or 6-membered aromatic (unsaturated) heterocyclic ring having two nitrogen atoms; (5) a 5-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom together with either one oxygen or one sulfur atom; wherein the 5 or 6-membered heterocyclic rings are optionally substituted by (C_1-C_3)lower alkyl, halogen or (C_1-C_3)lower alkoxy;

the moiety:

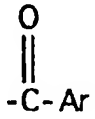


is a five membered aromatic (unsaturated) nitrogen containing heterocyclic ring wherein D, E and F are selected from carbon and nitrogen and wherein the carbon atoms may be optionally substituted by a substituent selected from halogen, (C_1-C_3)lower alkyl, hydroxy, -$COCCl_3$, -$COCF_3$,

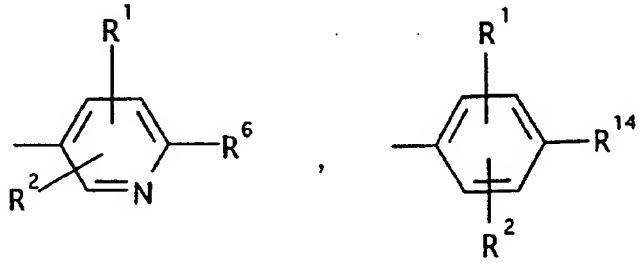


-CHO, amino, (C1-C3)lower alkoxy, (C1-C3)lower alkylamino, CONH-lower alkyl(C1-C3), and -CON[lower

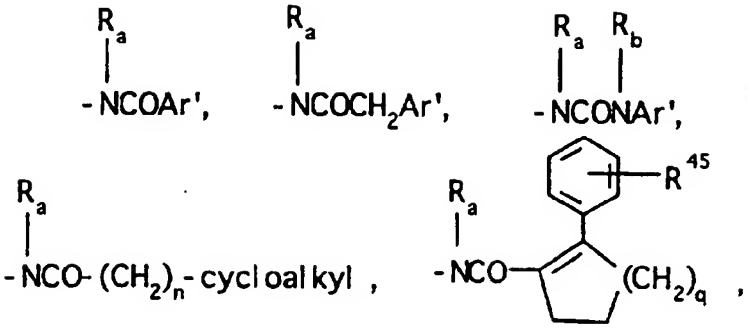
alkyl(C_1-C_3)]$_2$; q is one or two; R_b is independently selected from hydrogen, $-CH_3$ or $-C_2H_5$;
R_e is H, lower alkyl(C_1-C_3), hydroxyethyl, $-CH_2CO_2R^{50}$, $-CH_2C(CH_2OH)_3$;
R^{50} is H, lower alkyl(C_1-C_4);
R^3 is a moiety of the formula:

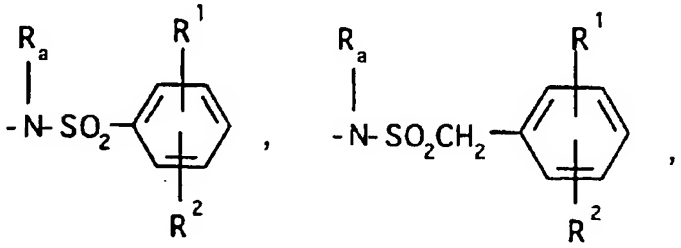


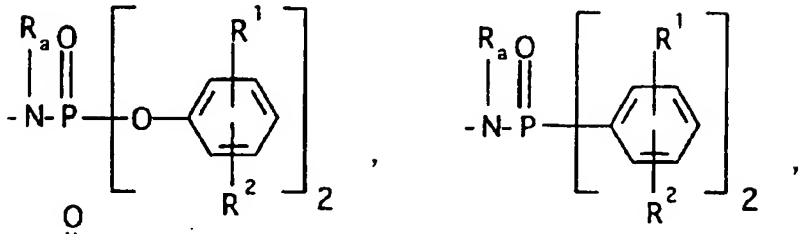
wherein Ar is a moiety selected from the group consisting of



wherein R^4 is selected from hydrogen, lower alkyl(C_1-C_3), -CO lower alkyl(C_1-C_3);
R^1 and R^2 are independently selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy, hydroxy and halogen; R^5 is selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy and halogen; R^6 is selected from (a) moieties of the formulae:







-NH-C(=O)-O-lower alkyl(C_3-C_8) straight or branched,

-NH-C(=O)-lower alkyl(C_3-C_8) straight or branched,

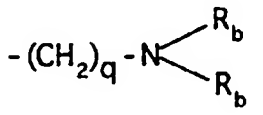
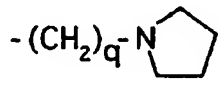
-$NHSO_2$-lower alkyl(C_3-C_8) straight or branched,

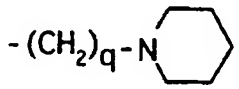
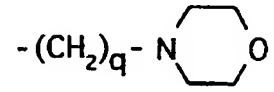
-NH-C(=O)-O-lower alkenyl(C_3-C_8) straight or branched,

-NH-C(=O)-lower alkenyl(C_3-C_8) straight or branched,

-$NHSO_2$-lower alkenyl(C_3-C_8) straight or branched,

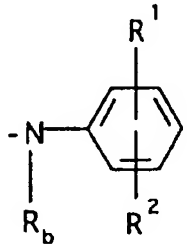
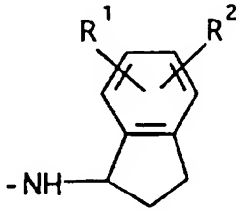
wherein cycloalkyl is defined as C_3-C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; R_a is independently selected from hydrogen, $-CH_3$, $-C_2H_5$,


,

,

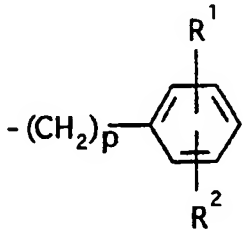
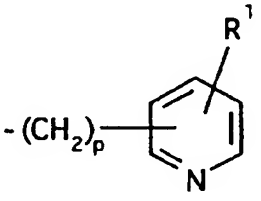

,

,

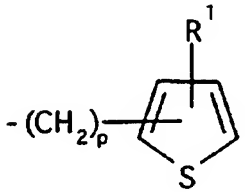
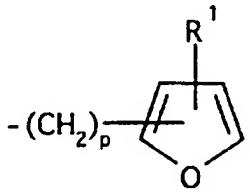
$-(CH_2)_q$-O-lower alkyl(C_1-C_3) and $-CH_2CH_2OH$, q is one or two, and R_1, R_2 and R_b are as hereinbefore defined;

(b) moieties of the formula:

,

,


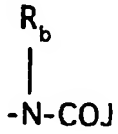
wherein R^7 is lower alkyl(C_3-C_8), lower alkenyl(C_3-C_8), $-(CH_2)_p$-cycloalkyl(C_3-C_6),


,

,

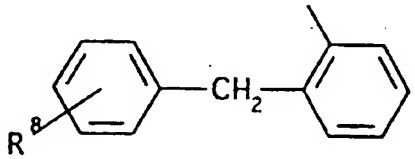

,


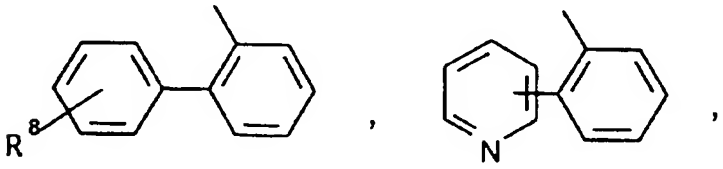
wherein p is one to five and X is selected from O, S, NH, NCH_3; wherein R^1 and R^2 are as hereinbefore defined;

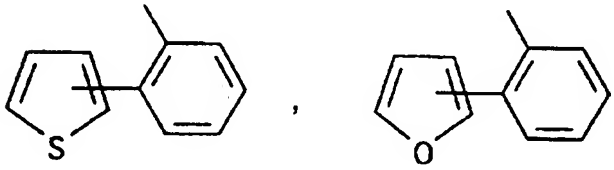
(c) a moiety of the formula:



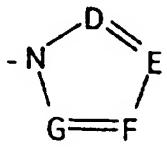
wherein J is R_a, lower alkyl(C_3-C_8) branched or unbranched, lower alkenyl(C_3-C_8) branched or unbranched, O-lower alkyl(C_3-C_8) branched or unbranched, -O-lower alkenyl(C_3-C_8) branched or unbranched, tetrahydrofuran, tetrahydrothiophene, the moieties:





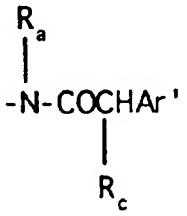


or $-CH_2-K'$ wherein K' is (C_1-C_3) lower alkoxy, halogen, tetrahydrofuran, tetrahydrothiophene or the heterocyclic ring moiety:

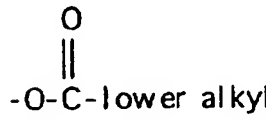


wherein D, E, F and G are selected from carbon or nitrogen and wherein the carbon atoms may be optionally substituted with halogen, (C_1-C_3)lower alkyl, hydroxy, -CO-lower alkyl(C_1-C_3), CHO, (C_1-C_3)lower alkoxy, -CO_2-lower alkyl(C_1-C_3), and R_a and R_b are as hereinbefore defined;

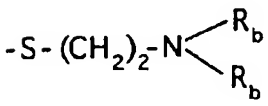
(d) a moiety of the formula:



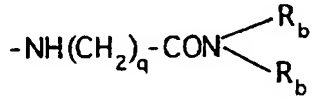
wherein R_c is selected from halogen, (C_1-C_3) lower alkyl, -O-lower alkyl(C_1-C_3), OH,



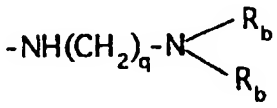
-O-C-lower alkyl(C_1-C_3), -S-lower alkyl(C_1-C_3),



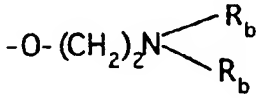
,



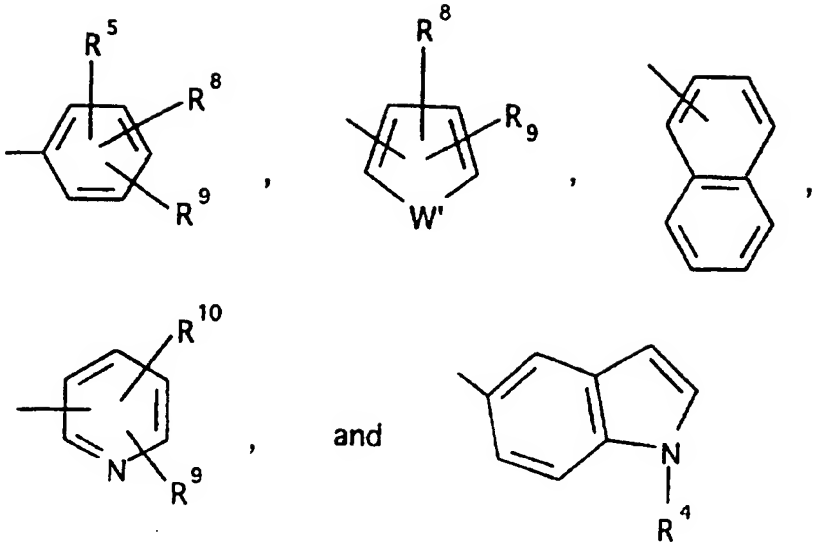
,



,

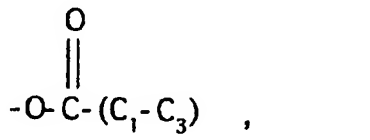


wherein R_a and R_b are as hereinbefore defined and Ar' is selected from moieties of the formula:



wherein W' is selected from O, S, NH, N-lower alkyl(C_1-C_3), NHCO-lower alkyl(C_1-C_3), and NSO_2lower alkyl(C_1-C_3);

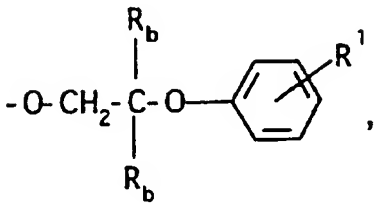
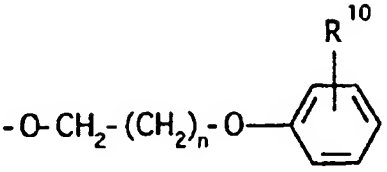
R^8 and R^9 are independently selected from hydrogen, lower alkyl(C_1-C_3), -S-lower alkyl(C_1-C_3), halogen, -NH-lower alkyl(C_1-C_3), -N-[lower alkyl(C_1-C_3)]2, $-OCF_3$, -OH, -CN, $-S-CF_3$, $-NO_2$, $-NH_2$, O-lower alkyl(C_1-C_3),



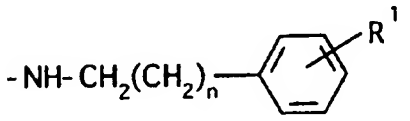
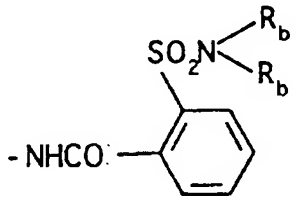
$-N(R_b)(CH_2)_vN(R_b)2$, and CF_3 wherein v is one to three and;

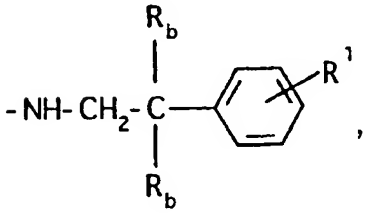
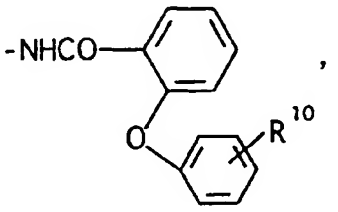
R^{10} is selected from hydrogen, halogen and lower alkyl(C_1-C_3); R^{14} is

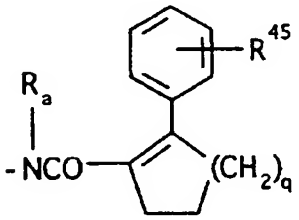
-O-lower alkyl (C_3-C_8) branched or unbranched,

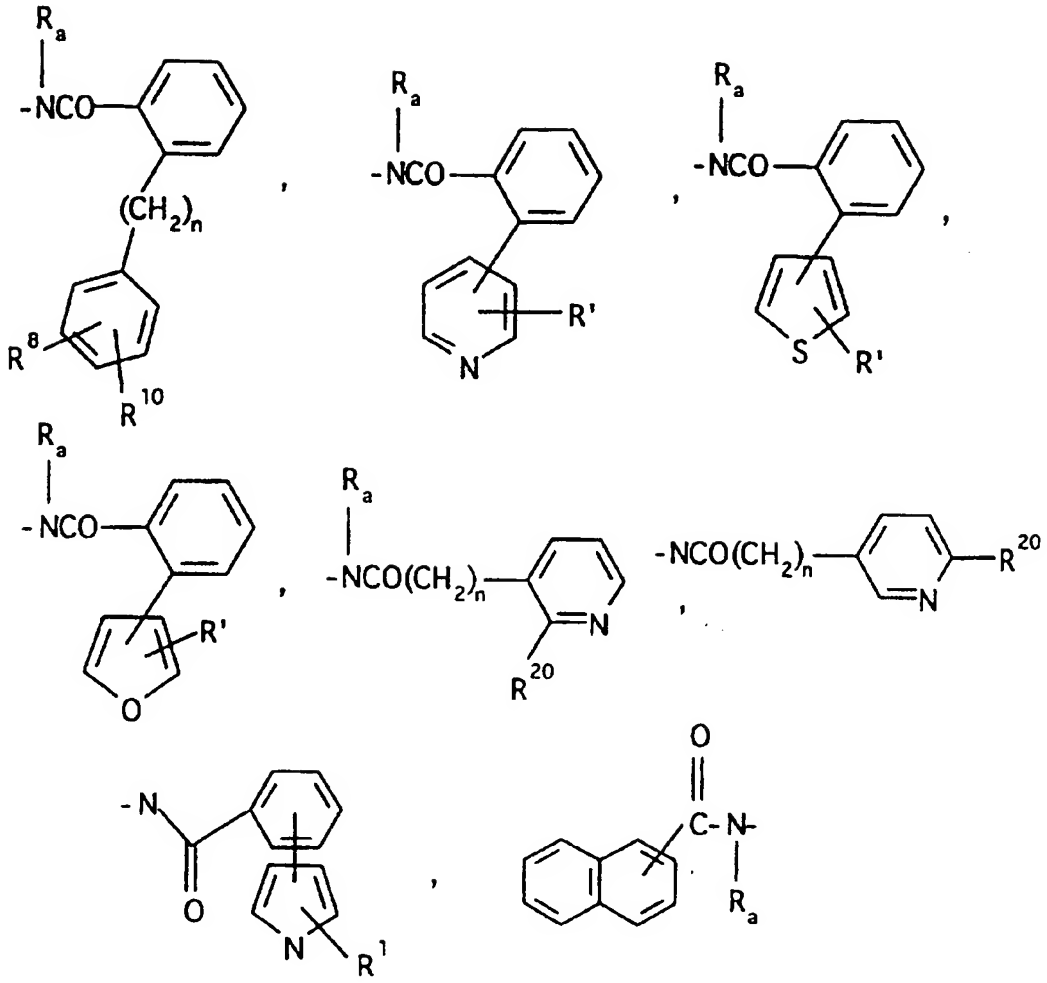

,

,

-NH lower alkyl (C_3-C_8) branched or unbranched,

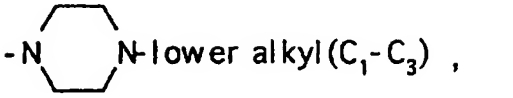

,



,

,


,

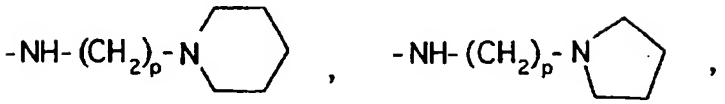


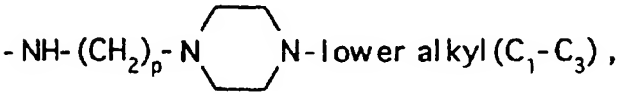
wherein n is 0 or 1; q is 1 or 2; R_a is hydrogen, $-CH_3$ or $-C_2H_5$; R' is hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy and halogen; R^{45} is hydrogen, (C_1-C_3) lower alkyl, (C_1-C_3)-lower alkoxy and halogen; R^{20} is hydrogen, halogen, (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy, NH_2, $-NH(C_1-C_3)$lower alkyl, $-N-[(C_1-C_3)$lower alkyl$]_2$.

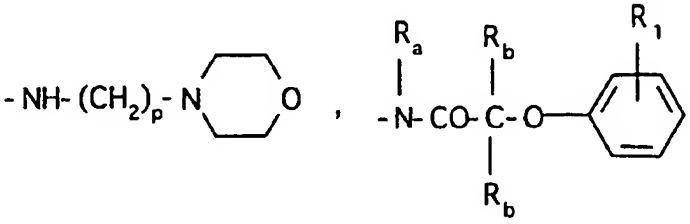


-NH-(CH$_2$)$_p$-NHlower alkyl(C$_1$-C$_3$),

-NH-(CH$_2$)$_p$-N[lower alkyl(C$_1$-C$_3$)]$_2$



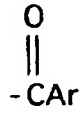




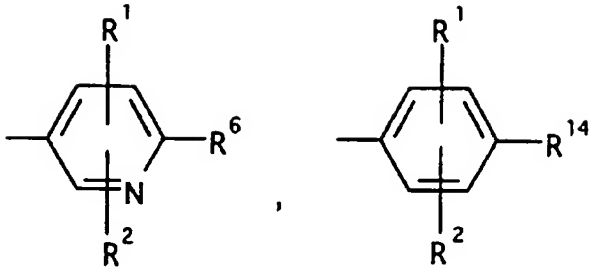
and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Within the group of the compounds defined by Formula I, certain subgroups of compounds are broadly preferred. Broadly preferred are those compounds wherein R3 is the moiety:

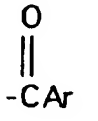


and Ar is selected from the moieties:



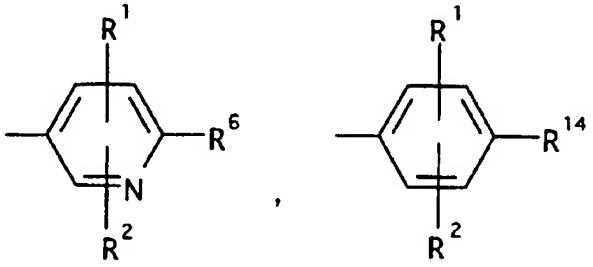
Y is $(CH_2)_n$ and n is one or zero;
wherein R^1, R^2, R^4, R^5, R^6 and R^{14} are as hereinbefore defined.

Especially preferred are compunds wherein R^3 is the moiety:



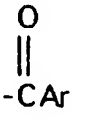
and

Ar is selected from the moieties:



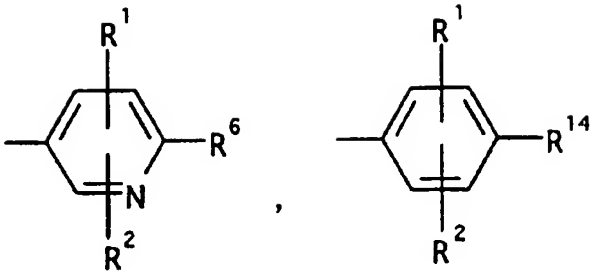
Y is $-(CH_2)_n$ and n is one and m is one;
wherein R^1, R^2, R^4, R^6 and R^{14} are as hereinbefore defined.

Especially preferred are compounds wherein R^3 is the moiety:



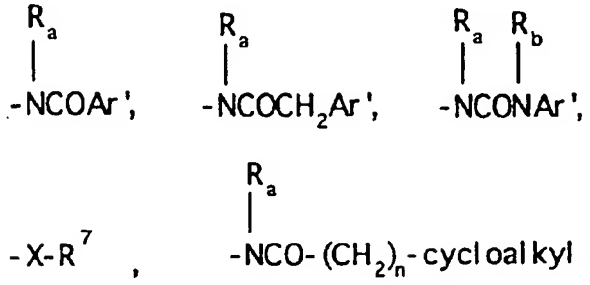
and

Ar is selected from the moieties:

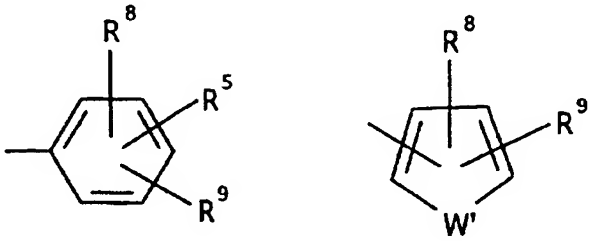


Y is $-(CH_2)_n$ and n is one or zero;

R^6 is



wherein cycloalkyl is defined as C_3-C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; and wherein X, R_a, R_b and R^{14} are as hereinbefore defined; and Ar' is selected from the moieties:

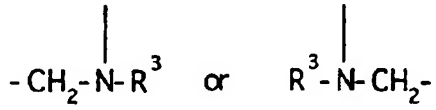


wherein R^8, R^9 and W' are as hereinbefore defined.

Also especially preferred are compounds wherein Y in Formula I is $-(CH_2)_n-$ and n is zero or one; A-B is

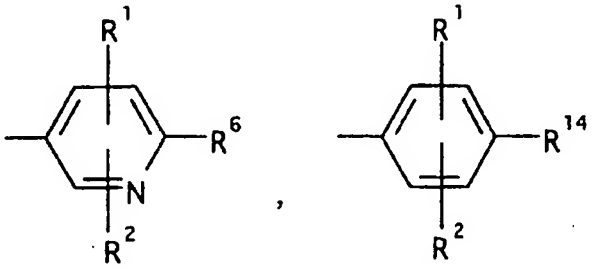
and R^1, R^2, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{14} are as hereinbefore defined; and m is an integer from 1-2.

The most preferred of the compounds of Formula I are those wherein Y is $-(CH_2)_n-$ and n is one; A-B is:

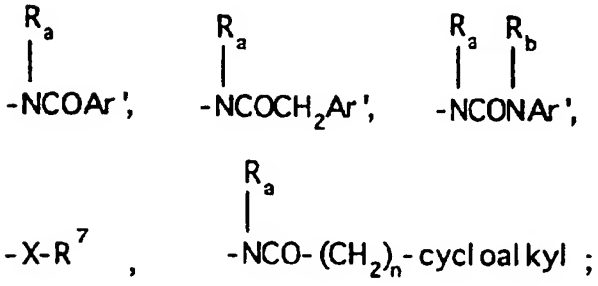


R_3 is the moiety:

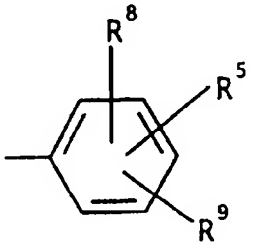
Ar is selected from the moieties:



R^6 is



$(CH_2)_n$-cycloalkyl wherein cycloalkyl is defined as C_3-C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; wherein X, R_a, R_b and R^{14} are as hereinbefore defined;
and Ar' is:

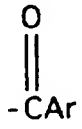


wherein R^5, R^8 and R^9 are as previously defined.

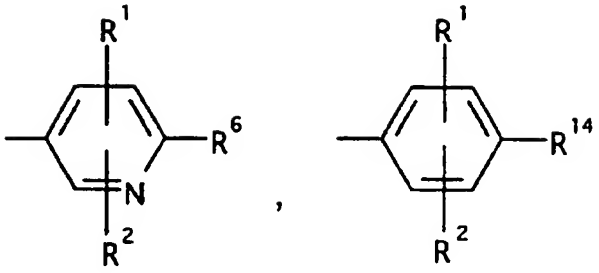
The most highly broadly preferred of the compounds of Formula I are those wherein Y is $-(CH_2)_n-$ and n is zero or one; wherein the moiety:

is a phenyl, substituted phenyl, thiophene, furan, pyrrole or pyridine ring;
A-B is:

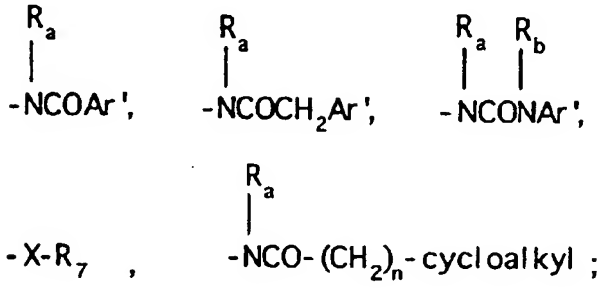
m is one when n is one and m is two when n is zero; D, E, F, R^1, R^2, R^4, R^5, R^7, R^8, R^9, R^{10} are as previously defined;
R_3 is the moiety:



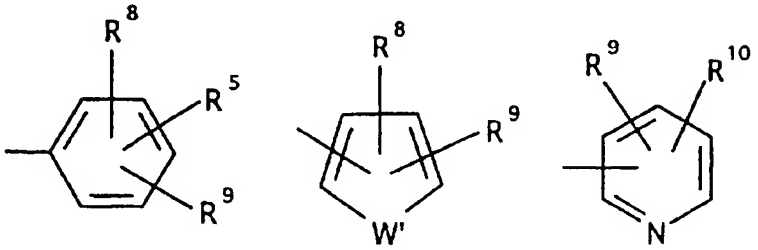
wherein Ar is selected from the moieties:



and R_6 is selected from the group:

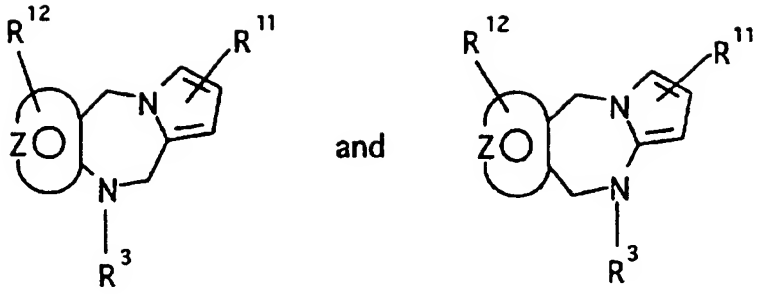


where Ar' is selected from the group:



and R^{14}, X, W', R_a, R_b and cycloalkyl are as previously described.

More particularly preferred are compounds of the formulae:

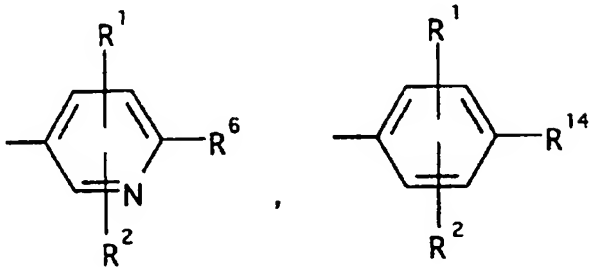


wherein the moiety:

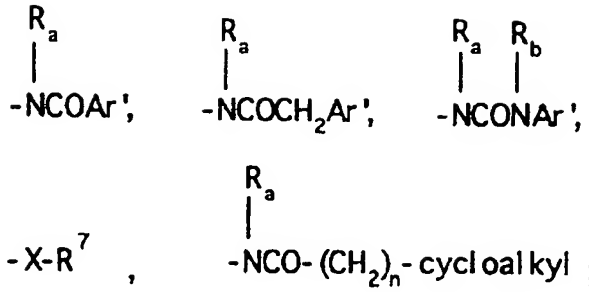
is selected from a phenyl, thiophene, furan, pyrrole, or pyridine ring;

R^3 is the moiety:

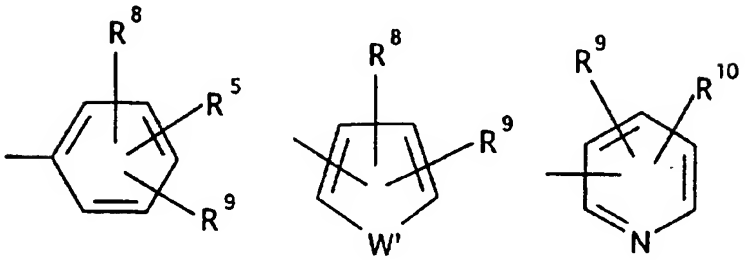
wherein Ar is selected from the moieties:



R^6 is

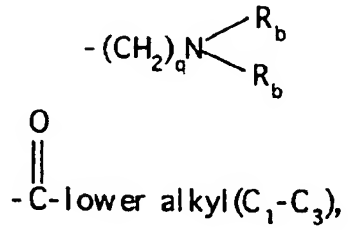


and Ar' is selected from the moieties:



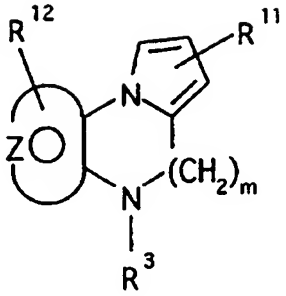
wherein X, R_a, R_b, R^5, R^7, R^8, R^9, R^{14}, cycloalkyl and W' are as hereinbefore described;

R^{11} is selected from hydrogen, halogen, (C_1-C_3) lower alkyl, hydroxy,

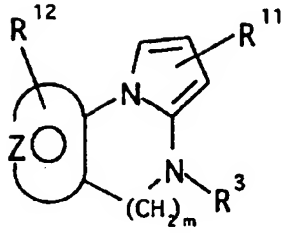


-CHO, and (C_1-C_3)lower alkoxy; and R^{12} is selected from hydrogen, (C_1-C_3)lower alkyl, halogen and (C_1-C_3) lower alkoxy.

Also particularly preferred are compounds of the formulae:



and



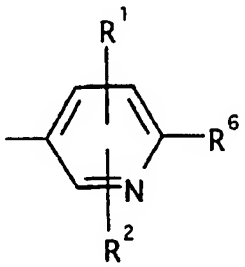
wherein m is one or two;

the moiety:

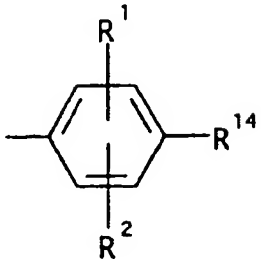
is selected from a phenyl, thiophene, furan, pyrrole or pyridine ring;

R^3 is the moiety:

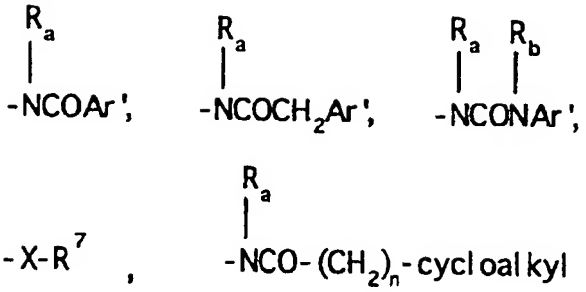
wherein Ar is selected from the moieties:



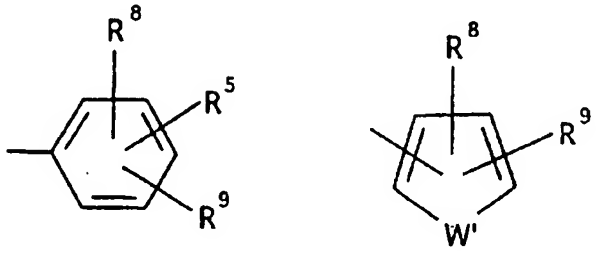
,



R^6 is

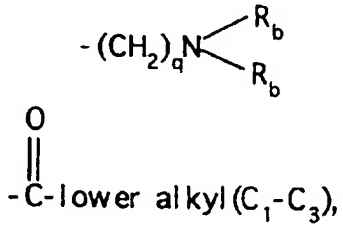


$(CH_2)_n$ cycloalkyl; Ar' is selected from the moieties:



wherein X, R_a, R_b, R^5, R^6, R^8, R^9, R^{14}, cycloalkyl and W' are as hereinbefore defined;

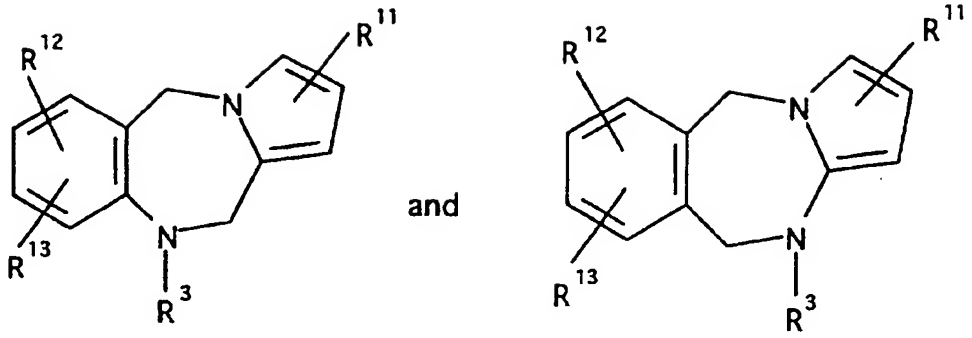
R^{11} is selected from hydrogen, halogen, (C_1-C_3) lower alkyl, hydroxy,



-CHO, and (C_1-C_3) lower alkoxy; and

R^{12} is selected from hydrogen, (C_1-C_3) lower alkyl, halogen and (C_1-C_3) lower alkoxy.

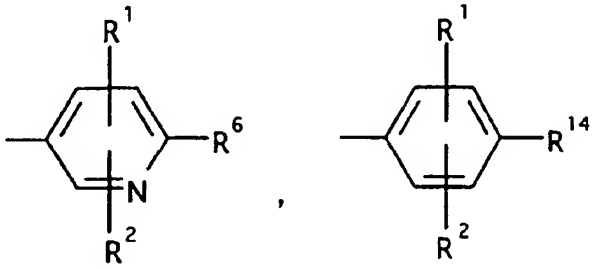
More particularly preferred are compounds of the formulae:



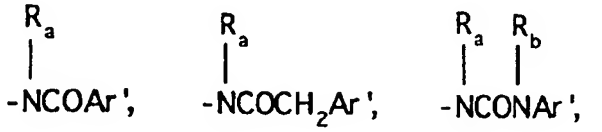
and

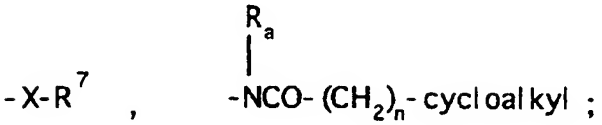
R^3 is the moiety:

wherein Ar is selected from the moieties:

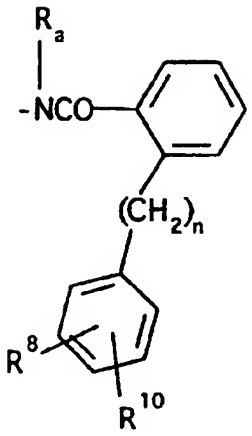


R^6 is

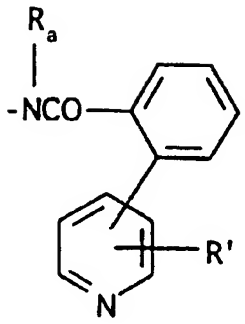




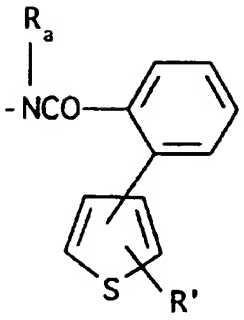
R^{14} is



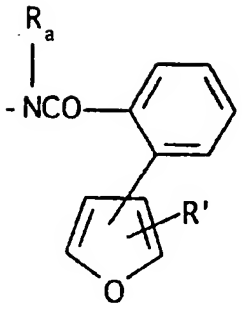
,



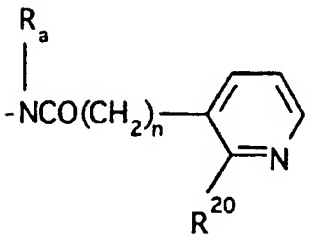
,



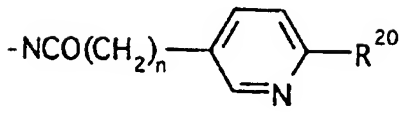
,



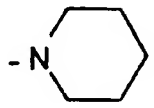
,



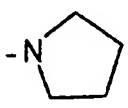
,



wherein n is 0 or 1; R_a is hydrogen, $-CH_3$ or $-C_2H_5$; R' is hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy and halogen; R^{20} is hydrogen, halogen, (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy, NH_2, $-NH$(C_1-C_3)lower alkyl, $-N$-[(C_1-C_3)lower alkyl]$_2$,

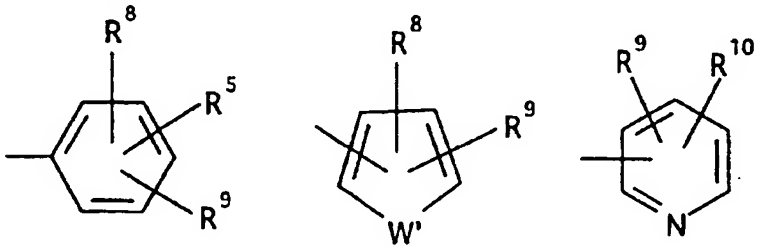


,



,

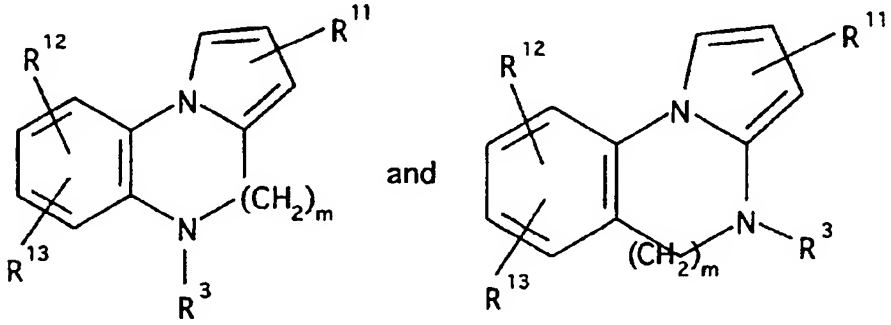
wherein cycloalkyl is defined as C_3-C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; R_b is hydrogen; R_a is independently selected from hydrogen, $-CH_3$, $-C_2H_5$ or $-(CH_2)_qN(CH_3)_2$; Ar' is selected from the moieties:



wherein q, X, R_a, R_b, R^5, R^7, R^8, R^9, R^{10}, R^{11} and W' are as hereinbefore described;

R^{12} and R^{13} are independently selected from hydrogen, (C_1-C_3) lower alkyl, halogen, amino, (C_1-C_3) lower alkoxy or (C_1-C_3) lower alkylamino.

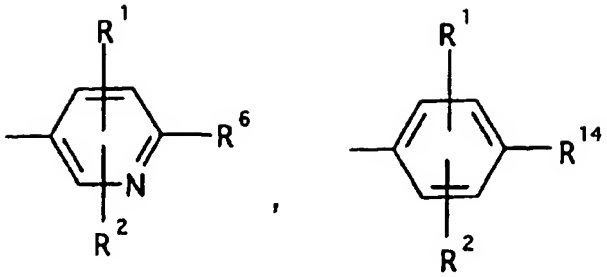
Also particularly preferred are compounds of the formulae:



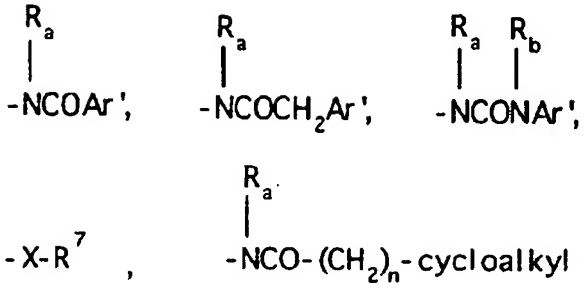
wherein m is one or two;

R^3 is the moiety:

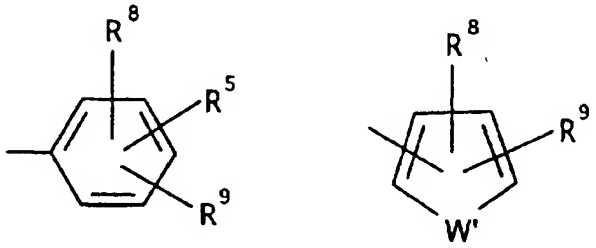
wherein Ar is selected from the moieties:



R^6 is



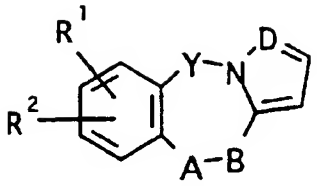
wherein cycloalkyl is defined as C_3-C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; R_b is hydrogen; R_a is independently selected from hydrogen, $-CH_3$, $-C_2H_5$ or $-(CH_2)_qN(CH_3)_2$; and Ar' is selected from the moieties:



wherein q, X, R_a, R_b, R^5, R^7, R^8, R^9, R^{11}, R^{14} and W' are as hereinbefore defined;

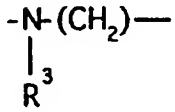
R^{12} and R^{13} are independently selected from hydrogen, (C_1-C_3) lower alkyl, halogen, amino, (C_1-C_3) lower alkoxy or (C_1-C_3) lower alkylamino.

The most highly broadly preferred of the compounds are those of the formula:



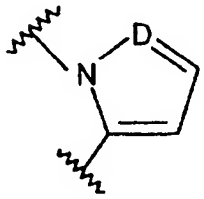
wherein Y is a moiety $-(CH_2)-$;

A-B is a moiety:



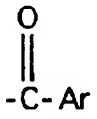
;

the moiety:

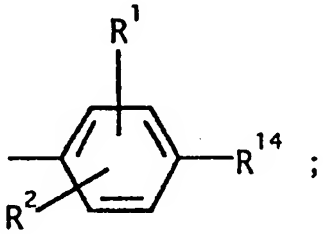


is a five membered aromatic (unsaturated) nitrogen containing heterocyclic ring optionally substituted by halogen, (C_1-C_3)lower alkyl, and $-(CH_2)_q-N(R_b)_2$ wherein D is carbon; q is 1 or 2; R_b is independently selected from hydrogen, $-CH_3$, and C_2H_5;

R^3 is a moiety of the formula:

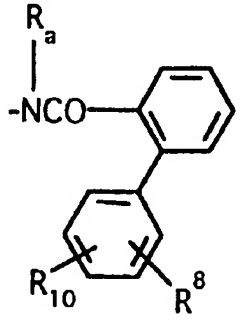


wherein Ar is a moiety selected from the group consisting of

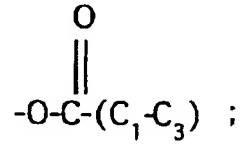


;

R^1 and R^2 are independently selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy and halogen; R^{14} is selected from a moiety of the formula:



wherein R_a is hydrogen; R^{10} is selected from hydrogen, halogen, and (C_1-C_3)lower alkyl; R^8 is selected from hydrogen, lower alkyl(C_1-C_3), -S-lower alkyl(C_1-C_3), halogen, -NH-lower alkyl(C_1-C_3), -N-[lower alkyl(C_1-C_3)]2, $-OCF_3$, -OH, -CN, $-S-CF_3$, $-NO_2$, $-NH_2$, O-lower alkyl(C_1-C_3), CF_3, and



;

and the pharmaceutically acceptable salts, esters and pro-drug forms thereof.